

**IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF DELAWARE**

TAKEDA PHARMACEUTICALS U.S.A., INC.,

Plaintiff,

v.

WEST-WARD PHARMACEUTICAL  
CORPORATION, HIKMA AMERICAS INC., and  
HIKMA PHARMACEUTICALS PLC,

Defendants.

Civil Action No. 14-cv-1268-SLR

**FIRST AMENDED COMPLAINT FOR JUDGMENT OF  
PATENT INFRINGEMENT AND DEMAND FOR JURY TRIAL**

Plaintiff Takeda Pharmaceuticals U.S.A., Inc. (“Takeda”) files this Complaint for patent infringement against Defendants West-Ward Pharmaceutical Corporation (“West-Ward”) and Hikma Americas Inc. and Hikma Pharmaceuticals PLC (collectively, “Hikma”) and, in support thereof, alleges as follows.

**NATURE OF THE ACTION**

1. This action for patent infringement arises under the patent laws of the United States, Title 35 of the United States Code, including at least 35 U.S.C. § 271, based on Hikma’s and West-Ward’s marketing and sale in the United States of the branded product MITIGARE™ (colchicine) 0.6 mg capsules and the authorized generic version of MITIGARE™ (hereinafter, the “MITIGARE™ AG”) (collectively, the MITIGARE™ and MITIGARE™ AG products are referred to herein as the “MITIGARE™ Products”).

### **THE PARTIES**

2. Takeda is a Delaware corporation with its principal place of business at One Takeda Parkway, Deerfield, Illinois 60015. Takeda holds all right, title, and interest in each patent asserted in this action.

3. Upon information and belief, West-Ward is a corporation organized and existing under the laws of the State of Delaware with a principal place of business at 401 Industrial Way West, Eatontown, New Jersey 07724.

4. Upon information and belief, West-Ward acts as a domestic marketer, manufacturer, and distributor of drug products for sale and use throughout the United States for entities affiliated with Hikma Pharmaceuticals PLC. West-Ward's website (<http://www.west-ward.com/en/AboutUs.aspx>) states the following: "West-Ward Pharmaceuticals is one of the top generic prescription medication providers in the US offering both oral solid and injectable pharmaceuticals to a growing number of chain stores, wholesalers, distributors, health systems and government agencies. We are the US agent and subsidiary of Hikma Pharmaceuticals PLC."

5. West-Ward's website (<http://www.west-ward.com/en/Products.aspx>) lists the MITIGARE™ AG (referred to therein as "Colchicine Capsules") as available for purchase. The MITIGARE™ Products' labels identify West-Ward as the entity that manufactures the MITIGARE™ Products.

6. Upon information and belief, Hikma Pharmaceuticals PLC ("Hikma Pharmaceuticals") is a company incorporated in the United Kingdom with a place of business at 13 Hanover Square, London, W1S 1HL, United Kingdom. Hikma Pharmaceuticals is a worldwide pharmaceutical company in the business of developing and manufacturing branded and generic drugs.

7. Upon information and belief, West-Ward is a wholly-owned subsidiary of Eurohealth (U.S.A.) Inc. and its parent, Hikma Pharmaceuticals. According to Hikma Pharmaceuticals' website (<http://www.hikma.com/en/about-hikma/our-businesses.aspx>), Hikma Pharmaceuticals' generics business in the United States "operates as West-Ward Pharmaceuticals, a domestic marketer and manufacturer of generic pharmaceutical products."

8. Upon information and belief, Hikma Americas Inc. ("Hikma Americas") is a company incorporated in the State of Tennessee with a place of business at 5865 Ridgeway Center Parkway, Suite 300, Memphis, Tennessee, 38120. Upon information and belief, Hikma Americas is a wholly-owned subsidiary of Hikma Pharmaceuticals.

9. Upon information and belief, since January 2015, Hikma Americas has sold and/or offered for sale, and continues to sell and/or offer for sale, the branded MITIGARE™ product in the United States, including in this District. Hikma Americas' website ([www.hikma-americas.com](http://www.hikma-americas.com)) lists MITIGARE™ as a product available for purchase. The MITIGARE™ product label identifies Hikma Americas as the entity that MITIGARE™ is "manufactured for."

### **JURISDICTION AND VENUE**

10. This Court has subject matter jurisdiction over this matter pursuant to 28 U.S.C. §§ 1331 and 1338(a).

11. This Court has personal jurisdiction over West-Ward because, among other reasons, it is a Delaware corporation, it has extensive contacts with the State of Delaware, and West-Ward regularly does business in this district.

12. West-Ward is subject to personal jurisdiction in this District by virtue of, *inter alia*, its incorporation under the laws of the State of Delaware, and its conduct of business in this District. Upon information and belief, West-Ward develops, formulates, manufactures, markets, and sells drug products throughout the United States, including Delaware, and Delaware is a

likely destination of West-Ward's products. Upon information and belief, West-Ward has active pharmacy wholesaler and controlled substance distributor and manufacturer licenses in Delaware.

13. Upon information and belief, since January 2015, West-Ward has sold and offered for sale, and continues to sell and offer for sale, the MITIGARE™ AG product in Delaware. Upon information and belief, West-Ward has purposely availed itself of the rights and benefits of the laws of the State of Delaware, and has engaged in substantial and continuous contacts with the State of Delaware.

14. Hikma Americas is subject to personal jurisdiction in this District because, *inter alia*, alone and/or together with West-Ward (which is incorporated under the laws of the State of Delaware), Hikma Americas has, on information and belief, purposefully availed itself of the rights and benefits of Delaware law by engaging in systematic and continuous contacts with Delaware. Upon information and belief, Hikma Americas, together with West-Ward and Hikma Pharmaceuticals, regularly and continuously transacts business within the State of Delaware, including, but not limited to, receiving pharmaceuticals from West-Ward for distribution within the United States generally, and within this District.

15. Additionally, the Hikma Americas website provides specific instructions regarding how to place an order for MITIGARE™. Upon information and belief, since January 2015, Hikma Americas has sold and/or offered for sale, and continues to sell and/or offer for sale, the branded MITIGARE™ product in the United States, including in this District. Upon information and belief there is no restriction on the sale of MITIGARE™ to residents of the State of Delaware, and residents in this District are freely able to access the Hikma Americas website to secure purchase of MITIGARE™.

16. Hikma Pharmaceuticals is subject to personal jurisdiction in this District because, *inter alia*, alone and/or together with its agent West-Ward (which is incorporated under the laws of the State of Delaware), Hikma Pharmaceuticals has purposefully availed itself of the rights and benefits of Delaware law by engaging in systematic and continuous contacts with Delaware. Upon information and belief, Hikma Pharmaceuticals, together with West-Ward, regularly and continuously transacts business within the State of Delaware, including, but not limited to, shipping pharmaceuticals to West-Ward from locations outside the United States for distribution by West-Ward within the United States generally, and within this District specifically.

17. In the alternative, this Court has personal jurisdiction over Hikma Pharmaceuticals under Fed. R. Civ. P. 4(k)(2) because this action arises under federal law and, upon information and belief, Hikma Pharmaceuticals is not subject to the general jurisdiction of the courts of any state and the exercise of personal jurisdiction over Hikma Pharmaceuticals is consistent with the Constitution and the laws of the United States.

18. Venue is proper in this District under 28 U.S.C. §§ 1391(b) and (c), and 1400(b).

### **STATEMENT OF FACTS RELEVANT TO ALL COUNTS**

#### **I. COLCRYS<sup>®</sup>**

19. COLCRYS<sup>®</sup> is primarily used to prevent and treat gout flares. Gout is a type of severe arthritis typically characterized by extremely painful “flares” (severe and sudden attacks of pain, redness, inflammation, and/or tenderness in joints) resulting from a build-up of uric acid. COLCRYS<sup>®</sup> is the only oral single-ingredient colchicine product approved by the FDA to treat and prevent gout flares.

20. The FDA approved COLCRYS<sup>®</sup> for marketing in the United States under New Drug Application (“NDA”) Nos. 22-351, 22-352 and 22-353 pursuant to section 505(b) of the Federal Food Drug and Cosmetics Act, 21 U.S.C. § 355(b).

21. In 2009, as a result of extensive research by Mutual Pharmaceutical Company, Inc. (“Mutual”), a former affiliate of Takeda, the FDA for the first time approved an oral single-active-ingredient colchicine product: COLCRYS®. Through its groundbreaking research, Mutual discovered important new information about colchicine, including previously unknown information concerning safety and efficacy, tolerability, dangerous side effects, and interactions with other medicines and substances.

22. Prior to COLCRYS®, there was no FDA-approved application demonstrating the safety and effectiveness of oral single-ingredient colchicine. The lack of FDA-reviewed data regarding oral single-ingredient colchicine was particularly troublesome because colchicine is potentially toxic. FDA has reported more than 160 deaths associated with oral colchicine. Accordingly, to better understand the toxicities, Mutual developed its own formulation and conducted numerous studies to support the safe and effective use of an oral single-ingredient colchicine product.

23. One of Mutual’s clinical studies, the Acute Gout Flare Receiving Colchicine Evaluation (“AGREE”) trial, provided important new information on the optimal dose of colchicine for treatment of gout flares. Traditionally, oral colchicine has been dosed for the treatment of gout flares by administering an initial dose of one to two tablets followed by additional doses every one to two hours until pain is relieved or until “nausea, vomiting, or diarrhea develops.” The usual dose totaled between 4 and 8 mg of colchicine, which was expected to result in toxicity-related side effects such as diarrhea or vomiting.

24. The AGREE trial completely upended the conventional wisdom. The trial was a double-blind, placebo-controlled, multicenter, dose-comparison study involving 575 trial participants that compared the effects of the “traditional” dose versus a lower dose of just 1.8 mg

total. The AGREE trial proved that the lower-dose regimen is just as effective as the higher traditional-dose regimen but without the serious adverse events of the higher dose. Based on Mutual's trial, the FDA approved Mutual's colchicine product with the low-dose regimen as safe and effective for the treatment of gout flares. The COLCRYS<sup>®</sup> low-dose regimen is in the FDA-approved product label attached as Exhibit A.

25. In 2012, the American College of Rheumatology ("ACR") issued guidelines for management of gout. The ACR recommends treating an acute gout flare by using a loading dose of 1.2 mg of colchicine, followed by 0.6 mg 1 hour later, and then, 12 hours later, resuming 0.6 mg prophylactic dosing once or twice daily, unless dose adjustment is necessary. The ACR guidelines adopt Takeda's low-dose regimen. The ACR recommendation remains the standard of care for the use of colchicine to treat acute gout flares. The ACR guidelines are attached as Exhibit B.

26. Mutual also conducted multiple studies regarding potential adverse drug interactions involving colchicine. Mutual researched numerous drug interactions that could result in unsafe levels of colchicine and even death. Mutual discovered, for example, that coadministering colchicine with clarithromycin could increase colchicine blood levels by nearly 230%. Due to Mutual's work, potentially dangerous interactions have been identified and characterized, and doctors and patients are now better informed. As a result of Mutual's research, appropriate dosing reductions to reduce the risk of an adverse reaction during concomitant administration with other agents, and the corresponding dose adjustment information, is included in the approved labeling for COLCRYS<sup>®</sup>.

27. Based on its studies, Mutual also discovered the correct dose adjustments for the safe use of colchicine with strong and moderate CYP3A4 inhibitors, P-gp inhibitors, and

protease inhibitors. The new dosing information is important to prevent unnecessary toxicity and even death and is included in the approved labeling for COLCRYS<sup>®</sup>. For example, the dose adjustment table in the COLCRYS<sup>®</sup> labeling provides that the prophylactic dose of colchicine, when used with a strong CYP3A4 inhibitor such as clarithromycin, should be adjusted from 0.6 mg twice per day to 0.3 mg once per day, which can be accomplished by altering the frequency and amount of a 0.6 mg dose. If the original intended prophylactic dose is 0.6 mg once a day, then the dose should be adjusted to 0.3 mg once every other day, which can be accomplished by altering the frequency and amount of a 0.6 mg dose. The COLCRYS<sup>®</sup> labeling also provides dose adjustments when coadministered with ketoconazole, verapamil, ritonavir, clarithromycin, and other drugs.

## **II. TAKEDA'S COLCRYS<sup>®</sup> PATENTS**

28. Takeda is the lawful owner of all right, title, and interest in and to the following United States patents, including the right to sue and to recover for infringement thereof, which contain one or more claims covering methods of use of COLCRYS<sup>®</sup>.

A. United States Patent Number 7,964,647 (“the ’647 Patent”), titled “COLCHICINE COMPOSITIONS AND METHODS,” a copy of which is attached hereto as Exhibit C and incorporated herein by reference as though set forth in full, which was duly and legally issued June 21, 2011, naming Matthew Davis as the inventor.

B. United States Patent Number 7,964,648 (“the ’648 Patent”), titled “METHODS FOR CONCOMITANT ADMINISTRATION OF COLCHICINE AND A SECOND ACTIVE AGENT,” a copy of which is attached hereto as Exhibit D and incorporated herein by reference as though set forth in full, which was duly and legally issued June 21, 2011, naming Matthew Davis as the inventor.

C. United States Patent Number 7,981,938 (“the ’938 Patent”), titled “COLCHICINE COMPOSITIONS AND METHODS,” a copy of which is attached hereto as Exhibit E and incorporated herein by reference as though set forth in full, which was duly and legally issued July 19, 2011, naming Matthew Davis as the inventor.

D. United States Patent Number 8,097,655 (“the ’655 Patent”), titled “METHODS FOR CONCOMITANT ADMINISTRATION OF COLCHICINE AND MACROLIDE ANTIBIOTICS,” a copy of which is attached hereto as Exhibit F and incorporated herein by reference as though set forth in full, which was duly and legally issued January 17, 2012, naming Matthew Davis as the inventor.

E. United States Patent Number 8,440,722 (“the ’722 Patent”), titled “METHODS FOR CONCOMITANT ADMINISTRATION OF COLCHICINE AND A SECOND ACTIVE AGENT,” a copy of which is attached hereto as Exhibit G and incorporated herein by reference as though set forth in full, which was duly and legally issued May 14, 2013, naming Matthew Davis as the inventor.

F. United States Patent Number 8,093,297 (“the ’297 Patent”), titled “METHODS FOR CONCOMITANT ADMINISTRATION OF COLCHICINE AND A SECOND ACTIVE AGENT,” a copy of which is attached hereto as Exhibit H and incorporated herein by reference as though set forth in full, which was duly and legally issued January 10, 2012, naming Matthew Davis as the inventor.

G. United States Patent Number 8,415,395 (“the ’395 Patent”), titled “COLCHICINE COMPOSITIONS AND METHODS,” a copy of which is attached hereto as Exhibit I and incorporated herein by reference as though set forth in full, which was duly and legally issued April 9, 2013, naming Matthew Davis as the inventor.

H. United States Patent Number 7,619,004 (“the ’004 patent”), titled “METHODS FOR CONCOMITANT ADMINISTRATION OF COLCHICINE AND MACROLINE ANTIBIOTICS,” a copy of which is attached hereto as Exhibit J and incorporated herein by reference as though set forth in full, which was duly and legally issued November 17, 2009, naming Matthew Davis as the inventor.

29. The ’648, ’655, ’722, ’297, and ’004 Patents are collectively referred to herein as the “drug-drug interaction patents” or “DDI Patents.”

30. The ’647, ’938, and ’395 Patents are collectively referred to herein as the “Acute Gout Treatment Patents.”

31. All of the above-listed patents are collectively referred to herein as the “COLCRYS® Patents.”

### **III. HIKMA’S AND WEST-WARD’S ACTIONS GIVING RISE TO THIS SUIT**

#### **A. THE MITIGARE™ PRODUCTS**

32. On or about October 5, 2012, Hikma Pharmaceuticals, with the assistance of West-Ward, submitted an NDA to the FDA, pursuant to Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for the approval to market and sell an oral single-ingredient colchicine product.

33. On September 26, 2014, the FDA approved NDA No. 204820 for the use of MITIGARE™ (colchicine) 0.6 mg capsules for the prophylaxis of gout flares.

34. Hikma’s and West-Ward’s MITIGARE™ Products contain the same active ingredient, colchicine, as COLCRYS®. Hikma’s and West-Ward’s MITIGARE™ Products also use the same route of administration (oral) and dosage strength (0.6 mg) as COLCRYS®. COLCRYS® and the MITIGARE™ Products all consist of 0.6 mg colchicine and the pharmacological properties of these drug products are the same. A copy of the MITIGARE™

product label is attached as Exhibit K. A copy of the MITIGARE™ AG product label is attached as Exhibit L. The MITIGARE™ AG product label is essentially identical to the MITIGARE™ product label, except that the MITIGARE™ AG product is referred to in the label as “colchicine capsules” rather than MITIGARE™.

35. COLCRYS® is approved for both prophylaxis and treatment of acute gout flares, while MITIGARE™ is approved only for prophylaxis. Nevertheless, the same 0.6 mg of colchicine can and is being used for either prophylaxis or treatment of acute gout flares. *See* Ex. M (Kaiser Permanente MITIGARE™ medication guide) (“The recommended dose is 1.2 milligrams at the first sign of an attack, followed by 0.6 milligrams one hour later. The maximum recommended dose is 1.8 milligrams taken over a 1-hour period.”).

**B. ALLEGATIONS RELEVANT TO HIKMA’S AND WEST-WARD’S INDUCED INFRINGEMENT OF THE ACUTE GOUT TREATMENT PATENTS**

**i. The MITIGARE™ and MITIGARE™ AG Product Labels**

36. With respect to acute treatment, upon information and belief, Hikma and West-Ward know and intend that healthcare providers will prescribe the MITIGARE™ Products for the treatment of acute gout flares according to the COLCRYS® product label and the ACR guidelines (i.e., a loading dose of 1.2 mg of colchicine, followed by 0.6 mg 1 hour later). The MITIGARE™ product label instructs patients: “If you have a gout flare while taking Mitigare™, tell your healthcare provider.” Ex. K at Medication Guide; *see also* Ex. L at Medication Guide (“If you have a gout flare while taking colchicine capsules, tell your healthcare provider”).

37. The only reference in the MITIGARE™ and MITIGARE™ AG product labels to the treatment of acute gout flares is a statement that “[t]he safety and effectiveness of MITIGARE™ [or “colchicine capsules”] for acute treatment of gout flares during prophylaxis

has not been studied.” Although Hikma and West-Ward may not have performed studies specifically directed to measure the safety and effectiveness of its 0.6 mg colchicine *capsule* product to treat acute gout flares, they know that Mutual did study the safety and effectiveness of its pharmacologically-identical 0.6 mg colchicine *tablet* product in treating acute gout flares, as described in the COLCRYS<sup>®</sup> product labeling. Reflecting such knowledge, in 2011, Hikma and West-Ward filed an opposition to a Citizen Petition filed by Mutual that discussed Mutual’s AGREE clinical trial and its low-dose regimen.

38. The Medication Guides for the MITIGARE<sup>™</sup> and MITIGARE<sup>™</sup> AG products do not instruct patients to refrain from taking MITIGARE for treatment of acute gout flares. Nor do they prescribe the proper dosage of MITIGARE for treating acute flares. Instead, they instruct patients who experience a gout flare while taking the MITIGARE<sup>™</sup> Products to inform their healthcare provider.

39. The MITIGARE<sup>™</sup> Products contain the same amount of colchicine as COLCRYS<sup>®</sup>. The COLCRYS<sup>®</sup> product labeling sets forth the low-dose regimen invented by Mutual for treating acute gout flares, and the ACR has endorsed that low-dose regimen as the standard of care for treating flares with colchicine. Hikma and West-Ward know and intend, or at a minimum are willfully blind to the fact, that at least some patients using the MITIGARE<sup>™</sup> Products will also use the MITIGARE<sup>™</sup> Products to treat acute gout flares by following the low-dose regimen found on the COLCRYS<sup>®</sup> product insert.

## **ii. FDA Correspondence**

40. Hikma’s and West-Ward’s intent that healthcare providers prescribe the MITIGARE<sup>™</sup> Products for the treatment of acute gout flares according to the COLCRYS<sup>®</sup> product label and the ACR guidelines is further demonstrated by Hikma’s and West-Ward’s correspondence with the FDA during the approval process leading to NDA No. 204820.

41. The FDA recognized the high likelihood that a drug suitable both for the treatment and the prophylaxis of acute gout flares likely would be prescribed for both. Thus, the FDA informed Hikma and West-Ward that they should inform healthcare providers that its product was suitable for acute gout flare treatment as well as for prophylaxis: “the labeling for a single-ingredient colchicine product should inform healthcare providers that a lower-dose regimen is adequate to treat an acute gout flare that may occur during chronic colchicine use, in the event of a need for acute-on-chronic treatment with colchicine.” The FDA later explained that it “included [reference to] acute treatment of gout flares during prophylaxis” in the product label because, “if Mitigare is being used for prophylaxis, it may be natural for the provider to use it for acute treatment as well.”

42. Rather than explicitly disclaim the use of MITIGARE for acute gout flare treatment, the method covered by Takeda’s patents, Hikma and West-Ward simply stated in the final MITIGARE™ product label that the “safety and effectiveness of MITIGARE™ for acute treatment of gout flares during prophylaxis has not been studied” and instructed patients: “If you have a gout flare while taking Mitigare™, tell your healthcare provider.” *See* Ex. K at § 1 and Medication Guide; *see also* Ex. L at § 1 and Medication Guide (same with respect to the MITIGARE™ AG product). Upon information and belief, Hikma and West-Ward thereby intended to encourage and facilitate the use of MITIGARE to treat acute gout flares in accordance with Takeda’s patented methods.

**iii. Marketing and Sales Activities**

43. Hikma and West-Ward launched MITIGARE™ in the United States on October 3, 2014. Upon information and belief, Hikma and West-Ward launched the MITIGARE™ AG on January 9, 2015.

44. On October 5, 2014, Takeda filed a motion with this Court seeking a temporary restraining order (“TRO”) to preserve the status quo while the parties briefed, and this Court considered, Takeda’s motion for a preliminary injunction. On October 9, 2014, this Court entered a memorandum order granting Takeda’s motion for a TRO. On November 4, 2014, this Court entered a memorandum order denying Takeda’s motion for a preliminary injunction, but enjoining Hikma and West-Ward from selling the MITIGARE™ Products during the pendency of Takeda’s expedited appeal to the United States Court of Appeals for the Federal Circuit. On January 9, 2015, the United States Court of Appeals for the Federal Circuit affirmed this Court’s order denying Takeda’s motion for a preliminary injunction and vacated the injunction pending appeal ordered by this Court.

45. Upon information and belief, since this Court’s injunction was vacated, Hikma and West-Ward have manufactured, advertised, promoted, marketed, offered to sell, and sold the MITIGARE™ Products in the United States and continue to do so. On January 9, 2015, in response to the competitive pressures of Hikma’s and Westward’s MITIGARE products, Takeda launched an authorized generic version of COLCRYS® (COLCRYS® AG). Upon information and belief, Hikma and West-Ward manufacture, advertise, promote, market, offer to sell, and sell the MITIGARE™ Products to compete directly with COLCRYS® and COLCRYS® AG.

46. Upon information and belief, Hikma’s and West-Ward’s goal is to drive the conversion of the colchicine market from COLCRYS® and COLCRYS® AG to the MITIGARE® AG product, irrespective of the indication for which the product is being used. Upon information and belief, Hikma and West-Ward intend to acquire a significant percentage of the colchicine market, including the acute gout flare market.

47. Upon information and belief, Hikma and West-Ward intend the MITIGARE™ Products to be used by the same patients who are currently using COLCRYS® to treat and prevent gout flares.

48. When used to treat acute gout flares, only three 0.6 mg tablets of colchicine need be taken. *See* Ex. A at §§ 1 and 2.1 (instructing patients to treat acute gout flares by prescribing 1.2 mg (two pills) at the first sign of a flare, followed by 0.6 mg (one pill) one hour later). In contrast, when used for prophylaxis, MITIGARE™ is to be taken once or twice per day for a period of three to six months, for a total of 30-360 capsules within six months or less. *See* Exs. I and J at §§ 1 and 2.1 (instructing patients to take 1-2 pills per day for prophylaxis). Upon information and belief, MITIGARE™ sales representatives have informed prescribers that thirty capsules of MITIGARE™ or the MITIGARE™ AG product could last a patient up to one year, demonstrating Hikma's and West-Ward's intent to sell the MITIGARE™ Products for the treatment of acute gout flares.

49. Upon information and belief, MITIGARE™ sales representatives have also explicitly informed prescribers that MITIGARE™ or the MITIGARE™ AG product can be used to treat acute gout flares.

50. Upon information and belief, Hikma and West-Ward are soliciting contracts with national health insurance providers wherein MITIGARE™ and/or the MITIGARE™ AG product is the sole source of single-ingredient oral colchicine on the formulary, excluding COLCRYS® or COLCRYS® AG, including for the treatment of acute gout flares in accordance with Takeda's patented methods.

51. For example, upon information and belief, Hikma and West-Ward have entered into at least two such sole-source contracts with health care provider Kaiser Permanente

(“Kaiser”) and health insurance provider UnitedHealthcare, and Hikma and West-Ward are attempting to secure additional such sole-source contracts, including with the U.S. Department of Veterans Affairs. Such contracts effectively guarantee that, for all patients covered by these insurance providers, the only single-ingredient oral colchicine option available to them for the treatment of acute gout flares will be MITIGARE™ or the MITIGARE™ AG product.

52. Upon information and belief, healthcare providers and patients will administer MITIGARE™ and the MITIGARE™ AG products in accordance with Takeda’s patented dosing regimen for the treatment of acute gout flares. As noted above, upon information and belief, one of Hikma’s and West-Ward’s sole-source contracts is with Kaiser Permanente, one of the nation’s largest managed healthcare organizations. Kaiser’s medication guide currently contains dosing instructions for acute treatment that describe Takeda’s patented method. *See* Ex. M (“The recommended dose is 1.2 milligrams at the first sign of an attack, followed by 0.6 milligrams one hour later. The maximum recommended dose is 1.8 milligrams taken over a 1-hour period.”). Kaiser’s medication guide does not contain any dosing instructions for prophylactic use, which is the only FDA-approved use for MITIGARE™. Upon information and belief, Kaiser physicians generally follow the dosing regimens set forth in Kaiser’s medication guide in prescribing medications to their patients.

53. Upon information and belief, Hikma and West-Ward became aware of the contents of Kaiser’s MITIGARE™ medication guide either during or shortly following the conclusion of their negotiations of their sole source contract with Kaiser, and failed either to inform Kaiser that MITIGARE™ could not properly be prescribed for acute gout flare treatment as specified in that guide, or to take any action to prevent such infringing use. The Kaiser medication guide thus illustrates that Hikma and West-Ward know and intend, or are at a

minimum are willfully blind to the fact, that healthcare organizations, physicians, and pharmacists will use MITIGARE™ to treat patients for acute gout flares in accordance with the claimed methods in the Acute Gout Treatment Patents.

54. As set forth in the preceding paragraphs, by intending, or being willfully blind to, the use of Takeda's patent-protected low-dose regimen, Hikma and West-Ward actively induce infringement of one or more claims of the '938, '647, and '395 patents.

**C. ALLEGATIONS RELEVANT TO HIKMA'S AND WEST-WARD'S  
INDUCED INFRINGEMENT OF THE DDI PATENTS**

**i. The MITIGARE™ and MITIGARE™ AG Product Labels**

55. The MITIGARE™ and MITIGARE™ AG product labels instruct doctors or patients, when coadministering MITIGARE™ with CYP3A4 or P-gp inhibitors, that "the dose of MITIGARE™ should be adjusted by either reducing the daily dose or reducing the dose frequency, and the patient should be monitored for colchicine toxicity." See Exs. K and L at §§ 7.1 and 7.2. These labels expressly name clarithromycin, ketoconazole, and verapamil as CYP3A4 inhibitors for which a dose reduction is necessary, but do not specify the amount by which the daily dose of colchicine should be reduced.

56. Hikma and West-Ward know that Mutual studied dose adjustments of colchicine in the presence of CYP3A4 and P-gp inhibitors and that dose reduction instructions are contained in the COLCRYS® product label.

57. Upon information and belief, Hikma and West-Ward know and intend, or are willfully blind to the fact that, because the MITIGARE™ and MITIGARE™ AG product labels fail to specify how to reduce the dose or dose frequency when the MITIGARE™ Products are concomitantly administered with clarithromycin, ketoconazole, verapamil, and ritonavir, at least some doctors and patients will consult the dose regimens set forth in the COLCRYS® product

labeling, and adjust the colchicine dosing according to the instructions in the FDA-approved COLCRYS<sup>®</sup> label.

**ii. FDA Correspondence**

58. Hikma's and West-Ward's intent or willful blindness to the fact that healthcare providers prescribe the MITIGARE<sup>™</sup> Products concomitantly with clarithromycin, ketoconazole, verapamil, and ritonavir, and adjust the colchicine dosing according to the patented methods set forth in the COLCRYS<sup>®</sup> label is further demonstrated by Hikma's and West-Ward's correspondence with the FDA during the approval process leading to NDA No. 204820.

59. As reflected in FDA meeting minutes, West-Ward initially argued to the FDA that a "specific dose reduction scheme(s) would be inappropriate in colchicine product labeling," and that "the solution to address a drug-drug interaction concern with colchicine would be to refrain from using colchicine or the interacting drug." The FDA, however, rejected this approach, responding that "the labeling for a single-ingredient colchicine product would need to include specific recommended dose modifications in the event of a need for concomitant administration with interacting drugs (moderate CYP3A4 inhibitors, strong CYP3A4 inhibitors, and P-gp inhibitors)."

60. West-Ward then proposed labeling containing an instruction that patients who were concomitantly administering colchicine should follow a dosing regimen different from the patented COLCRYS<sup>®</sup> method, but without any indication that such reduced dosing would be therapeutically effective: "In the rare case that both the colchicine and the CYP3A4 and/or P-gp inhibitor are truly necessary, decrease the dose of colchicine to 0.6 mg once or twice per week . . . ." As reflected in FDA meeting minutes, the FDA again denied West-Ward's request, finding it "[un]clear how [West-Ward] derived [this] dose modification recommendation[]" and expressing

“concern[] that disparate recommendations in the labeling for Colcris (colchicine) and the proposed labeling for [West-Ward’s] product ... may cause patient and prescriber confusion with respect to drug-drug interactions.” On the FDA’s suggestion, West-Ward then conducted its own drug-drug interaction studies. FDA documents reflect that West-Ward selected different CYP3A4/P-gp inhibitors than those studied by Mutual and discussed in the Colcris<sup>®</sup> label, apparently because Mutual had already determined and patented the appropriate dosing reductions for concomitant administration of colchicine with those drugs. However, the FDA found the results of Hikma and West-Ward’s drug-drug interaction studies inconclusive, “mak[ing] it difficult to know how to label the product.”

61. Ultimately, the FDA departed from its initial position that the MITIGARE<sup>™</sup> label “would need to include specific recommended dose modifications,” and approved a label with a vague general instruction to “reduc[e] the daily dose or reduc[e] the dose frequency” when concomitantly administered with CYP3A4 or P-gp inhibitors. *See* Ex. K at § 7.1.

62. The only specific instructions for how to reduce colchicine dosages when the drug is coadministered with CYP3A4 or P-gp inhibitors are the patented dosing reductions contained in the COLCRYS<sup>®</sup> label, which the ACR has adopted as the standard of care for colchicine treatment. Upon information and belief, Hikma and West-Ward knew and intended, or were willfully blind to the fact that at least some physicians, pharmacists, or healthcare organizations, would consult the FDA-approved COLCRYS<sup>®</sup> label and/or the ACR guidelines to determine the specific amount of dose reductions required for concomitant administration with CYP3A4 and/or P-gp inhibitors.

63. As discussed in the preceding paragraphs, by intending, or being willfully blind to use of Takeda's patent-protected adjusted-dosing regimens, Hikma and West-Ward actively induce infringement of one or more claims of the '655, '648, '722, '297, and '004 patents.

**COUNT I**

**(Infringement of the '647 Patent Under 35 U.S.C. § 271(b))**

64. Paragraphs 1 to 63 are incorporated herein as set forth above.

65. Upon information and belief, Hikma and West-Ward have induced and are actively inducing others to directly infringe the claims of the '647 Patent. Specifically, Hikma and West-Ward encourage others to sell, offer to sell, and/or use the MITIGARE™ Products within the United States according to the patented methods through sale of their products to drug wholesalers and retailers through their distributors. Such uses occur at the active behest of Hikma and West-Ward, and with Hikma's and West-Ward's intent, knowledge, and encouragement. Specifically, Hikma and West-Ward induce physicians to prescribe, and patients to use, the MITIGARE™ Products according to the patented method of claim 1 of the '647 Patent, therefore inducing infringement of claim 1 of the '647 Patent under 35 U.S.C. § 271(b).

66. Hikma's and West-Ward's acts of induced infringement have caused damage to Takeda, and Takeda is entitled to recover compensatory damages sustained as a result of Hikma's and West-Ward's wrongful acts. Unless enjoined by this Court, Hikma and West-Ward will continue to infringe the '647 Patent, continuing to damage Takeda and causing Takeda irreparable harm.

67. Takeda requests a judgment that Hikma's and West-Ward's manufacture, use, offer for sale, sale, and/or importation of the MITIGARE™ Products before the '647 Patent expires induces infringement of one or more claims of the '647 Patent.

**COUNT II**

**(Infringement of the '648 Patent Under 35 U.S.C. § 271(b))**

68. Paragraphs 1 to 67 are incorporated herein as set forth above.

69. Upon information and belief, Hikma and West-Ward have induced and are actively inducing others to directly infringe the claims of the '648 Patent. Specifically, Hikma and West-Ward encourage others to sell, offer to sell, and/or use the MITIGARE™ Products within the United States according to the patented methods through sale of their products to drug wholesalers and retailers through their distributors. Such uses occur at the active behest of Hikma and West-Ward, and with Hikma's and West-Ward's intent, knowledge, and encouragement. Specifically, Hikma and West-Ward induce physicians to prescribe, and patients to use, the MITIGARE™ Products according to the patented methods of the '648 Patent, therefore inducing infringement of the method claims of the '648 Patent under 35 U.S.C. § 271(b).

70. Hikma's and West-Ward's acts of induced infringement have caused damage to Takeda, and Takeda is entitled to recover compensatory damages sustained as a result of Hikma's and West-Ward's wrongful acts. Unless enjoined by this Court, Hikma and West-Ward will continue to infringe the '648 Patent, continuing to damage Takeda and causing Takeda irreparable harm.

71. Takeda requests a judgment that Hikma's and West-Ward's manufacture, use, offer for sale, sale, and/or importation of the MITIGARE™ Products before the '648 Patent expires induces infringement of one or more claims of the '648 Patent.

### **COUNT III**

#### **(Infringement of the '938 Patent Under 35 U.S.C. § 271(b))**

72. Paragraphs 1 to 71 are incorporated herein as set forth above.

73. Upon information and belief, Hikma and West-Ward have induced and are actively inducing others to directly infringe the claims of the '938 Patent. Specifically, Hikma and West-Ward encourage others to sell, offer to sell, and/or use the MITIGARE™ Products within the United States according to the patented methods through sale of their products to drug wholesalers and retailers through their distributors. Such uses occur at the active behest of Hikma and West-Ward, and with Hikma's and West-Ward's intent, knowledge, and encouragement. Specifically, Hikma and West-Ward induce physicians to prescribe, and patients to use, the MITIGARE™ Products according to the patented method of claim 1 of the '938 Patent, therefore inducing infringement of claim 1 of the '938 Patent under 35 U.S.C. § 271(b).

74. Hikma's and West-Ward's acts of induced infringement have caused damage to Takeda, and Takeda is entitled to recover compensatory damages sustained as a result of Hikma's and West-Ward's wrongful acts. Unless enjoined by this Court, Hikma and West-Ward will continue to infringe the '938 Patent, continuing to damage Takeda and causing Takeda irreparable harm.

75. Takeda requests a judgment that Hikma's and West-Ward's manufacture, use, offer for sale, sale, and/or importation of the MITIGARE™ Products before the '938 Patent expires induces infringement of one or more claims of the '938 Patent.

### **COUNT IV**

#### **(Infringement of the '655 Patent Under 35 U.S.C. § 271(b))**

76. Paragraphs 1 to 75 are incorporated herein as set forth above.

77. Upon information and belief, Hikma and West-Ward have induced and are actively inducing others to directly infringe the claims of the '655 Patent. Specifically, Hikma and West-Ward encourage others to sell, offer to sell, and/or use the MITIGARE™ Products within the United States according to the patented methods through sale of their products to drug wholesalers and retailers through their distributors. Such uses occur at the active behest of Hikma and West-Ward, and with Hikma's and West-Ward's intent, knowledge, and encouragement. Specifically, Hikma and West-Ward induce physicians to prescribe, and patients to use, the MITIGARE™ Products according to the patented methods of the '655 Patent, therefore inducing infringement of the method claims of the '655 Patent under 35 U.S.C. § 271(b).

78. Hikma's and West-Ward's acts of induced infringement have caused damage to Takeda, and Takeda is entitled to recover compensatory damages sustained as a result of Hikma's and West-Ward's wrongful acts. Unless enjoined by this Court, Hikma and West-Ward will continue to infringe the '655 Patent, continuing to damage Takeda and causing Takeda irreparable harm.

79. Takeda requests a judgment that Hikma's and West-Ward's manufacture, use, offer for sale, sale, and/or importation of the MITIGARE™ Products before the '655 Patent expires induces infringement of one or more claims of the '655 Patent.

### **COUNT V**

#### **(Infringement of the '722 Patent Under 35 U.S.C. § 271(b))**

80. Paragraphs 1 to 79 are incorporated herein as set forth above.

81. Upon information and belief, Hikma and West-Ward have induced and are actively inducing others to directly infringe the claims of the '722 Patent. Specifically, Hikma and West-Ward encourage others to sell, offer to sell, and/or use the MITIGARE™ Products

within the United States according to the patented methods through sale of their products to drug wholesalers and retailers through their distributors. Such uses occur at the active behest of Hikma and West-Ward, and with Hikma's and West-Ward's intent, knowledge, and encouragement. Specifically, Hikma and West-Ward induce physicians to prescribe, and patients to use, the MITIGARE™ Products according to the patented methods of the '722 Patent, therefore inducing infringement of the method claims of the '722 Patent under 35 U.S.C. § 271(b).

82. Hikma's and West-Ward's acts of induced infringement have caused damage to Takeda, and Takeda is entitled to recover compensatory damages sustained as a result of Hikma's and West-Ward's wrongful acts. Unless enjoined by this Court, Hikma and West-Ward will continue to infringe the '722 Patent, continuing to damage Takeda and causing Takeda irreparable harm.

83. Takeda requests a judgment that Hikma's and West-Ward's manufacture, use, offer for sale, sale, and/or importation of the MITIGARE™ Products before the '722 Patent expires induces infringement of one or more claims of the '722 Patent.

## **COUNT VI**

### **(Infringement of the '297 Patent Under 35 U.S.C. § 271(b))**

84. Paragraphs 1 to 83 are incorporated herein as set forth above.

85. Upon information and belief, Hikma and West-Ward have induced and are actively inducing others to directly infringe the claims of the '297 Patent. Specifically, Hikma and West-Ward encourage others to sell, offer to sell, and/or use the MITIGARE™ Products within the United States according to the patented methods through sale of their products to drug wholesalers and retailers through their distributors. Such uses occur at the active behest of Hikma and West-Ward, and with Hikma's and West-Ward's intent, knowledge, and

encouragement. Specifically, Hikma and West-Ward induce physicians to prescribe, and patients to use, the MITIGARE™ Products according to the patented methods of the '297 Patent, therefore inducing infringement of the method claims of the '297 Patent under 35 U.S.C. § 271(b).

86. Hikma's and West-Ward's acts of induced infringement have caused damage to Takeda, and Takeda is entitled to recover compensatory damages sustained as a result of Hikma's and West-Ward's wrongful acts. Unless enjoined by this Court, Hikma and West-Ward will continue to infringe the '297 Patent, continuing to damage Takeda and causing Takeda irreparable harm.

87. Takeda requests a judgment that Hikma's and West-Ward's manufacture, use, offer for sale, sale, and/or importation of the MITIGARE™ Products before the '297 Patent expires induces infringement of one or more claims of the '297 Patent.

## **COUNT VII**

### **(Infringement of the '395 Patent Under 35 U.S.C. § 271(b))**

88. Paragraphs 1 to 87 are incorporated herein as set forth above.

89. Upon information and belief, Hikma and West-Ward have induced and are actively inducing others to directly infringe the claims of the '395 Patent. Specifically, Hikma and West-Ward encourage others to sell, offer to sell, and/or use the MITIGARE™ Products within the United States according to the patented methods through sale of their products to drug wholesalers and retailers through their distributors. Such uses occur at the active behest of Hikma and West-Ward, and with Hikma's and West-Ward's intent, knowledge, and encouragement. Specifically, Hikma and West-Ward induce physicians to prescribe, and patients to use, the MITIGARE™ Products according to the patented methods of the '395 Patent,

therefore inducing infringement of the method claims of the '395 Patent under 35 U.S.C. § 271(b).

90. Hikma's and West-Ward's acts of induced infringement have caused damage to Takeda, and Takeda is entitled to recover compensatory damages sustained as a result of Hikma's and West-Ward's wrongful acts. Unless enjoined by this Court, Hikma and West-Ward will continue to infringe the '395 Patent, continuing to damage Takeda and causing Takeda irreparable harm.

91. Takeda requests a judgment that Hikma's and West-Ward's manufacture, use, offer for sale, sale, and/or importation of the MITIGARE™ Products before the '395 Patent expires induces infringement of one or more claims of the '395 Patent.

### **COUNT VIII**

#### **(Infringement of the '004 Patent Under 35 U.S.C. § 271(b))**

92. Paragraphs 1 to 91 are incorporated herein as set forth above.

93. Upon information and belief, Hikma and West-Ward have induced and are actively inducing others to directly infringe the claims of the '004 Patent. Specifically, Hikma and West-Ward encourage others to sell, offer to sell, and/or use the MITIGARE™ Products within the United States according to the patented methods through sale of their products to drug wholesalers and retailers through their distributors. Such uses occur at the active behest of Hikma and West-Ward, and with Hikma's and West-Ward's intent, knowledge, and encouragement. Specifically, Hikma and West-Ward induce physicians to prescribe, and patients to use, the MITIGARE™ Products according to the patented methods of the '004 Patent, therefore inducing infringement of the method claims of the '004 Patent under 35 U.S.C. § 271(b).

94. Hikma's and West-Ward's acts of induced infringement have caused damage to Takeda, and Takeda is entitled to recover compensatory damages sustained as a result of Hikma's and West-Ward's wrongful acts. Unless enjoined by this Court, Hikma and West-Ward will continue to infringe the '004 Patent, continuing to damage Takeda and causing Takeda irreparable harm.

95. Takeda requests a judgment that Hikma's and West-Ward's manufacture, use, offer for sale, sale, and/or importation of the MITIGARE™ Products before the '004 Patent expires induces infringement of one or more claims of the '004 Patent.

**PRAYER FOR RELIEF**

**WHEREFORE**, Takeda requests entry of judgment in its favor and against West-Ward, Hikma Americas, and Hikma Pharmaceuticals as follows:

A. A judgment that West-Ward, Hikma Americas, and Hikma Pharmaceuticals have induced infringement of one or more claims of the COLCRYS® Patents under 35 U.S.C. § 271(b) by the manufacture, use, offering to sell, and sale in, and importation into the United States of West-Ward's, Hikma Americas, and Hikma Pharmaceuticals' MITIGARE™ Products prior to the expiration of those patents;

B. A judgment that West-Ward, Hikma Americas, and Hikma Pharmaceuticals' infringement of the COLCRYS® Patents has been willful, that this is an exceptional case under 35 U.S.C. § 285, and that Takeda is entitled to its costs and reasonable attorney fees;

C. A permanent injunction enjoining West-Ward, Hikma Americas, and Hikma Pharmaceuticals, their officers, agents, servants, employees, licensees, representatives, and attorneys, and all other persons acting or attempting to act in active concert or participation

with it or acting on their behalf, from inducing physicians to prescribe, and patients to use, the MITIGARE™ Products according to the patented methods in the COLCRYS® Patents;

D. A permanent injunction enjoining West-Ward, Hikma Americas, and Hikma Pharmaceuticals, their officers, agents, servants, employees, licensees, representatives, and attorneys, and all other persons acting or attempting to act in active concert or participation with it or acting on their behalf, from maintaining or soliciting any sole-source contract pursuant to which the only single-ingredient oral colchicine option available to a patient under that sole-source contract for the treatment of acute gout flares, or for concomitant administration with clarithromycin, ketoconazole, ritonavir, or verapamil, is MITIGARE™ or the MITIGARE™ AG product;

E. An order that West-Ward, Hikma Americas, and Hikma Pharmaceuticals pay to Takeda damages in an amount adequate to compensate Takeda for those infringements, together with interest and costs to the full extent allowed under the law, in an amount to be determined at trial;

F. An order that West-Ward, Hikma Americas, and Hikma Pharmaceuticals pay to Takeda enhanced damages up to treble the amount as provided by 35 U.S.C. § 284.

G. Such other and further relief as the Court may deem just and proper.

#### **JURY DEMAND**

Pursuant to Fed. R. Civ. P. 38, Takeda hereby demands a trial by jury of all issues in this case that are so triable by right.

Date: September 9, 2015

**WOMBLE CARLYLE SANDRIDGE & RICE, LLP**

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**CERTIFICATE OF SERVICE**

I hereby certify that on September 9, 2015, I caused the foregoing to be electronically filed with the Clerk of the Court using CM/ECF which will send electronic notification of such filing to all registered participants.

Additionally, I hereby certify that true and correct copies of the foregoing were caused to be served on September 9, 2015 upon the following individuals via electronic mail:

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# EXHIBIT A

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use colchicine safely and effectively. See [full prescribing information](#) for COLCRYS.

**COLCRYS (colchicine, USP) tablets, for oral use**

Initial U.S. Approval: 1961

----- **RECENT MAJOR CHANGES** -----

Dosage and Administration  
Prophylaxis of Gout Flares ([2.1](#)) 11/2012

----- **INDICATIONS AND USAGE** -----

COLCRYS (colchicine, USP) tablets are an alkaloid indicated for:

- Prophylaxis and treatment of gout flares in adults ([1.1](#)).
- Familial Mediterranean fever (FMF) in adults and children 4 years or older ([1.2](#)).

COLCRYS is not an analgesic medication and should not be used to treat pain from other causes.

----- **DOSAGE AND ADMINISTRATION** -----

• **Gout Flares:**

**Prophylaxis of Gout Flares:** 0.6 mg once or twice daily in adults and adolescents older than 16 years of age ([2.1](#)). Maximum dose 1.2 mg/day.

**Treatment of Gout Flares:** 1.2 mg (two tablets) at the first sign of a gout flare followed by 0.6 mg (one tablet) one hour later ([2.1](#)).

- **FMF:** Adults and children older than 12 years 1.2 – 2.4 mg; children 6 to 12 years 0.9 – 1.8 mg; children 4 to 6 years 0.3 – 1.8 mg ([2.2](#), [2.3](#)).
  - Give total daily dose in one or two divided doses ([2.2](#)).
  - Increase or decrease the dose as indicated and as tolerated in increments of 0.3 mg/day, not to exceed the maximum recommended daily dose ([2.2](#)).

Colchicine tablets are administered orally without regard to meals.

See full prescribing information for dose adjustment regarding patients with impaired renal function ([2.5](#)), impaired hepatic function ([2.6](#)), the patient's age ([2.3](#), [8.5](#)) or use of coadministered drugs ([2.4](#)).

----- **DOSAGE FORMS AND STRENGTHS** -----

- 0.6 mg tablets ([3](#)).

----- **CONTRAINDICATIONS** -----

Patients with renal or hepatic impairment should not be given COLCRYS in conjunction with P-gp or strong CYP3A4 inhibitors ([5.3](#)). In these patients, life-threatening and fatal colchicine toxicity has been reported with colchicine taken in therapeutic doses ([7](#)).

----- **WARNINGS AND PRECAUTIONS** -----

- **Fatal overdoses** have been reported with colchicine in adults and children. Keep COLCRYS out of the reach of children ([5.1](#), [10](#)).
- **Blood dyscrasias:** myelosuppression, leukopenia, granulocytopenia, thrombocytopenia and aplastic anemia have been reported ([5.2](#)).
- Monitor for toxicity and if present consider temporary interruption or discontinuation of colchicine ([5.2](#), [5.3](#), [5.4](#), [6](#), [10](#)).
- **Drug interaction P-gp and/or CYP3A4 inhibitors:** Coadministration of colchicine with P-gp and/or strong CYP3A4 inhibitors has resulted in life-threatening interactions and death ([5.3](#), [7](#)).

- **Neuromuscular toxicity:** Myotoxicity including rhabdomyolysis may occur, especially in combination with other drugs known to cause this effect. Consider temporary interruption or discontinuation of COLCRYS ([5.4](#), [7](#)).

----- **ADVERSE REACTIONS** -----

**Prophylaxis of Gout Flares:** The most commonly reported adverse reaction in clinical trials for the prophylaxis of gout was diarrhea.

**Treatment of Gout Flares:** The most common adverse reactions reported in the clinical trial for gout were diarrhea (23%) and pharyngolaryngeal pain (3%).

**FMF:** Most common adverse reactions (up to 20%) are abdominal pain, diarrhea, nausea and vomiting. These effects are usually mild, transient and reversible upon lowering the dose ([6](#)).

**To report SUSPECTED ADVERSE REACTIONS, contact Takeda Pharmaceuticals America, Inc. at 1-877-825-3327 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

----- **DRUG INTERACTIONS** -----

Coadministration of P-gp and/or CYP3A4 inhibitors (e.g., clarithromycin or cyclosporine) have been demonstrated to alter the concentration of colchicine. The potential for drug-drug interactions must be considered prior to and during therapy. See full prescribing information for a complete list of reported and potential interactions ([2.4](#), [5.3](#), [7](#)).

----- **USE IN SPECIFIC POPULATIONS** -----

- In the presence of mild to moderate renal or hepatic impairment, adjustment of dosing is not required for treatment of gout flare, prophylaxis of gout flare and FMF, but patients should be monitored closely ([2.5](#), [8.6](#)).
- In patients with severe renal impairment for prophylaxis of gout flares, the starting dose should be 0.3 mg/day for gout flares, no dose adjustment is required, but a treatment course should be repeated no more than once every two weeks. In FMF patients, start with 0.3 mg/day, and any increase in dose should be done with close monitoring ([2.5](#), [8.6](#)).
- In patients with severe hepatic impairment, a dose reduction may be needed in prophylaxis of gout flares and FMF patients; while a dose reduction may not be needed in gout flares, a treatment course should be repeated no more than once every two weeks ([2.5](#), [2.6](#), [8.6](#), [8.7](#)).
- For patients undergoing dialysis, the total recommended dose for prophylaxis of gout flares should be 0.3 mg given twice a week with close monitoring. For treatment of gout flares, the total recommended dose should be reduced to 0.6 mg (one tablet) x 1 dose and the treatment course should not be repeated more than once every two weeks. For FMF patients, the starting dose should be 0.3 mg/day and dosing can be increased with close monitoring ([2.5](#), [8.6](#)).
- **Pregnancy:** Use only if the potential benefit justifies the potential risk to the fetus ([8.1](#)).
- **Nursing Mothers:** Caution should be exercised when administered to a nursing woman ([8.3](#)).
- **Geriatric Use:** The recommended dose of colchicine should be based on renal function ([2.5](#), [8.5](#)).

**See [17](#) for PATIENT COUNSELING INFORMATION and Medication Guide.**

**Revised: 11/2012**

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\*Sections or subsections omitted from the full prescribing information are not listed

## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

#### 1.1 Gout Flares

COLCRYS (colchicine, USP) tablets are indicated for prophylaxis and the treatment of acute gout flares.

- **Prophylaxis of Gout Flares:**  
COLCRYS is indicated for prophylaxis of gout flares.
- **Treatment of Gout Flares:**  
COLCRYS tablets are indicated for treatment of acute gout flares when taken at the first sign of a flare.

#### 1.2 Familial Mediterranean Fever (FMF)

COLCRYS (colchicine, USP) tablets are indicated in adults and children 4 years or older for treatment of familial Mediterranean fever (FMF).

### 2 DOSAGE AND ADMINISTRATION

The long-term use of colchicine is established for FMF and the prophylaxis of gout flares, but the safety and efficacy of repeat treatment for gout flares has not been evaluated. The dosing regimens for COLCRYS are different for each indication and must be individualized.

The recommended dosage of COLCRYS depends on the patient's age, renal function, hepatic function and use of coadministered drugs [see *Dose Modification for Coadministration of Interacting Drugs* (2.4)].

COLCRYS tablets are administered orally without regard to meals.

COLCRYS is not an analgesic medication and should not be used to treat pain from other causes.

#### 2.1 Gout Flares

##### Prophylaxis of Gout Flares

The recommended dosage of COLCRYS for prophylaxis of gout flares for adults and adolescents older than 16 years of age is 0.6 mg once or twice daily. The maximum recommended dose for prophylaxis of gout flares is 1.2 mg/day.

An increase in gout flares may occur after initiation of uric acid-lowering therapy, including pegloticase, febuxostat and allopurinol, due to changing serum uric acid levels resulting in mobilization of urate from tissue deposits. COLCRYS is recommended upon initiation of gout flare prophylaxis with uric acid-lowering therapy. Prophylactic therapy may be beneficial for at least the first six months of uric acid-lowering therapy.

##### Treatment of Gout Flares

The recommended dose of COLCRYS for treatment of a gout flare is 1.2 mg (two tablets) at the first sign of the flare followed by 0.6 mg (one tablet) one hour later. Higher doses have not been found to be more effective. The maximum recommended dose for treatment of gout flares is 1.8 mg over a one-hour period. COLCRYS may be administered for treatment of a gout flare during prophylaxis at doses not to exceed 1.2 mg (two tablets) at the first sign of the flare followed by 0.6 mg (one tablet) one hour later. Wait 12 hours and then resume the prophylactic dose.

## **2.2 FMF**

The recommended dosage of COLCRYS for FMF in adults is 1.2 mg to 2.4 mg daily.

COLCRYS should be increased as needed to control disease and as tolerated in increments of 0.3 mg/day to a maximum recommended daily dose. If intolerable side effects develop, the dose should be decreased in increments of 0.3 mg/day. The total daily COLCRYS dose may be administered in one to two divided doses.

## **2.3 Recommended Pediatric Dosage Prophylaxis and Treatment of Gout Flares**

COLCRYS is not recommended for pediatric use in prophylaxis or treatment of gout flares.

### **FMF**

The recommended dosage of COLCRYS for FMF in pediatric patients 4 years of age and older is based on age. The following daily doses may be given as a single or divided dose twice daily:

- Children 4 to 6 years: 0.3 mg to 1.8 mg daily
- Children 6 to 12 years: 0.9 mg to 1.8 mg daily
- Adolescents older than 12 years: 1.2 mg to 2.4 mg daily

## **2.4 Dose Modification for Coadministration of Interacting Drugs**

### **Concomitant Therapy**

Coadministration of COLCRYS with drugs known to inhibit CYP3A4 and/or P-glycoprotein (P-gp) increases the risk of colchicine-induced toxic effects ([Table 1](#)). If patients are taking or have recently completed treatment with drugs listed in Table 1 within the prior 14 days, the dose adjustments are as shown in the table below [see *Drug Interactions* ([7](#))].

<b>Table 1. COLCRYS Dose Adjustment for Coadministration with Interacting Drugs if no Alternative Available*</b>							
<b>Strong CYP3A4 Inhibitors†</b>							
<b>Drug</b>	<b>Noted or Anticipated Outcome</b>	<b>Gout Flares</b>				<b>FMF</b>	
		<b>Prophylaxis of Gout Flares</b>		<b>Treatment of Gout Flares</b>		<b>Original Intended Dosage</b>	<b>Adjusted Dose</b>
		<b>Original Intended Dosage</b>	<b>Adjusted Dose</b>	<b>Original Intended Dosage</b>	<b>Adjusted Dose</b>		
Atazanavir Clarithromycin Darunavir/ Ritonavir‡ Indinavir Itraconazole Ketoconazole Lopinavir/ Ritonavir‡ Nefazodone Nelfinavir Ritonavir Saquinavir Telithromycin Tipranavir/ Ritonavir‡	Significant increase in colchicine plasma levels*; fatal colchicine toxicity has been reported with clarithromycin, a strong CYP3A4 inhibitor. Similarly, significant increase in colchicine plasma levels is anticipated with other strong CYP3A4 inhibitors.	0.6 mg twice a day	0.3 mg once a day	1.2 mg (2 tablets) followed by 0.6 mg (1 tablet) 1 hour later. Dose to be repeated no earlier than 3 days.	0.6 mg (1 tablet) x 1 dose, followed by 0.3 mg (1/2 tablet) 1 hour later. Dose to be repeated no earlier than 3 days.	Maximum daily dose of 1.2 – 2.4 mg	Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day)
<b>Moderate CYP3A4 Inhibitors</b>							
<b>Drug</b>	<b>Noted or Anticipated Outcome</b>	<b>Gout Flares</b>				<b>FMF</b>	
		<b>Prophylaxis of Gout Flares</b>		<b>Treatment of Gout Flares</b>		<b>Original Intended Dosage</b>	<b>Adjusted Dose</b>
		<b>Original Intended Dosage</b>	<b>Adjusted Dose</b>	<b>Original Intended Dosage</b>	<b>Adjusted Dose</b>		
Amprenavir‡ Aprepitant Diltiazem Erythromycin Fluconazole Fosamprenavir‡ (pro-drug of Amprenavir) Grapefruit juice Verapamil	Significant increase in colchicine plasma concentration is anticipated. Neuromuscular toxicity has been reported with diltiazem and verapamil interactions.	0.6 mg twice a day	0.3 mg twice a day or 0.6 mg once a day	1.2 mg (2 tablets) followed by 0.6 mg (1 tablet) 1 hour later. Dose to be repeated no earlier than 3 days.	1.2 mg (2 tablets) x 1 dose. Dose to be repeated no earlier than 3 days.	Maximum daily dose of 1.2 – 2.4 mg	Maximum daily dose of 1.2 mg (may be given as 0.6 mg twice a day)
<b>P-gp Inhibitors‡</b>							
<b>Drug</b>	<b>Noted or Anticipated Outcome</b>	<b>Gout Flares</b>				<b>FMF</b>	
		<b>Prophylaxis of Gout Flares</b>		<b>Treatment of Gout Flares</b>		<b>Original Intended Dosage</b>	<b>Adjusted Dose</b>
		<b>Original Intended Dosage</b>	<b>Adjusted Dose</b>	<b>Original Intended Dosage</b>	<b>Adjusted Dose</b>		
Cyclosporine Ranolazine	Significant increase in colchicine plasma levels*; fatal colchicine toxicity has been reported with cyclosporine, a P-gp inhibitor. Similarly, significant increase in colchicine plasma levels is anticipated with other P-gp inhibitors.	0.6 mg twice a day	0.3 mg once a day	1.2 mg (2 tablets) followed by 0.6 mg (1 tablet) 1 hour later. Dose to be repeated no earlier than 3 days.	0.6 mg (1 tablet) x 1 dose. Dose to be repeated no earlier than 3 days.	Maximum daily dose of 1.2 – 2.4 mg	Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day)

\*For magnitude of effect on colchicine plasma concentrations [see *Pharmacokinetics* (12.3)]

†Patients with renal or hepatic impairment should not be given COLCRYS in conjunction with strong CYP3A4 or P-gp inhibitors [see *Contraindications* (4)]

‡When used in combination with Ritonavir, see dosing recommendations for strong CYP3A4 inhibitors [see *Contraindications* (4)]

<b>Table 2. COLCRYS Dose Adjustment for Coadministration with Protease Inhibitors</b>					
<b>Protease Inhibitor</b>	<b>Clinical Comment</b>	<b>w/Colchicine - Prophylaxis of Gout Flares</b>		<b>w/Colchicine - Treatment of Gout Flares</b>	<b>w/Colchicine - Treatment of FMF</b>
Atazanavir sulfate (Reyataz)	Patients with renal or hepatic impairment should not be given colchicine with Reyataz.	<b>Original dose</b>	<b>Adjusted dose</b>	0.6 mg (1 tablet) x 1 dose, followed by 0.3 mg (1/2 tablet) 1 hour later. Dose to be repeated no earlier than 3 days.	Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day)
		0.6 mg twice a day	0.3 mg once a day		
		0.6 mg once a day	0.3 mg once every other day		
Darunavir (Prezista)	Patients with renal or hepatic impairment should not be given colchicine with Prezista/ritonavir.	<b>Original dose</b>	<b>Adjusted dose</b>	0.6 mg (1 tablet) x 1 dose, followed by 0.3 mg (1/2 tablet) 1 hour later. Dose to be repeated no earlier than 3 days.	Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day)
		0.6 mg twice a day	0.3 mg once a day		
		0.6 mg once a day	0.3 mg once every other day		
Fosamprenavir (Lexiva) with Ritonavir	Patients with renal or hepatic impairment should not be given colchicine with Lexiva/ritonavir.	<b>Original dose</b>	<b>Adjusted dose</b>	0.6 mg (1 tablet) x 1 dose, followed by 0.3 mg (1/2 tablet) 1 hour later. Dose to be repeated no earlier than 3 days.	Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day)
		0.6 mg twice a day	0.3 mg once a day		
		0.6 mg once a day	0.3 mg once every other day		
Fosamprenavir (Lexiva)	Patients with renal or hepatic impairment should not be given colchicine with Lexiva/ritonavir.	<b>Original dose</b>	<b>Adjusted dose</b>	1.2 mg (2 tablets) x 1 dose. Dose to be repeated no earlier than 3 days.	Maximum daily dose of 1.2 mg (may be given as 0.6 mg twice a day)
		0.6 mg twice a day	0.3 mg twice a day or 0.6 mg once a day		
		0.6 mg once a day	0.3 mg once a day		
Indinavir (Crixivan)	Patients with renal or hepatic impairment should not be given colchicine with Crixivan.	<b>Original dose</b>	<b>Adjusted dose</b>	0.6 mg (1 tablet) x 1 dose, followed by 0.3 mg (1/2 tablet) 1 hour later. Dose to be repeated no earlier than 3 days.	Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day)
		0.6 mg twice a day	0.3 mg once a day		
		0.6 mg once a day	0.3 mg once every other day		
Lopinavir/Ritonavir (Kaletra)	Patients with renal or hepatic impairment should not be given colchicine with Kaletra.	<b>Original dose</b>	<b>Adjusted dose</b>	0.6 mg (1 tablet) x 1 dose, followed by 0.3 mg (1/2 tablet) 1 hour later. Dose to be repeated no earlier than 3 days.	Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day)
		0.6 mg twice a day	0.3 mg once a day		
		0.6 mg once a day	0.3 mg once every other day		
Nelfinavir mesylate (Viracept)	Patients with renal or hepatic impairment should not be given colchicine with Viracept.	<b>Original dose</b>	<b>Adjusted dose</b>	0.6 mg (1 tablet) x 1 dose, followed by 0.3 mg (1/2 tablet) 1 hour later. Dose to be repeated no earlier than 3 days.	Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day)
		0.6 mg twice a day	0.3 mg once a day		
		0.6 mg once a day	0.3 mg once every other day		
Ritonavir (Norvir)	Patients with renal or hepatic impairment should not be given colchicine with Norvir.	<b>Original dose</b>	<b>Adjusted dose</b>	0.6 mg (1 tablet) x 1 dose, followed by 0.3 mg (1/2 tablet) 1 hour later. Dose to be repeated no earlier than 3 days.	Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day)
		0.6 mg twice a day	0.3 mg once a day		
		0.6 mg once a day	0.3 mg once every other day		
Saquinavir mesylate (Invirase)	Patients with renal or hepatic impairment should not be given colchicine with Invirase/ritonavir.	<b>Original dose</b>	<b>Adjusted dose</b>	0.6 mg (1 tablet) x 1 dose, followed by 0.3 mg (1/2 tablet) 1 hour later. Dose to be repeated no earlier than 3 days.	Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day)
		0.6 mg twice a day	0.3 mg once a day		
		0.6 mg once a day	0.3 mg once every other day		
Tipranavir (Aptivus)	Patients with renal or hepatic impairment should not be given colchicine with Aptivus/ritonavir.	<b>Original dose</b>	<b>Adjusted dose</b>	0.6 mg (1 tablet) x 1 dose, followed by 0.3 mg (1/2 tablet) 1 hour later. Dose to be repeated no earlier than 3 days.	Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day)
		0.6 mg twice a day	0.3 mg once a day		
		0.6 mg once a day	0.3 mg once every other day		

Treatment of gout flares with COLCRYS is not recommended in patients receiving prophylactic dose of COLCRYS and CYP3A4 inhibitors.

## 2.5 Dose Modification in Renal Impairment

Colchicine dosing must be individualized according to the patient's renal function [see *Renal Impairment* (8.6)].

Cl<sub>cr</sub> in mL/minute may be estimated from serum creatinine (mg/dL) determination using the following formula:

$$\text{Cl}_{\text{cr}} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}} \times 0.85 \text{ for female patients}$$

### Gout Flares

#### **Prophylaxis of Gout Flares**

For prophylaxis of gout flares in patients with mild (estimated creatinine clearance [Cl<sub>cr</sub>] 50 to 80 mL/min) to moderate (Cl<sub>cr</sub> 30 to 50 mL/min) renal function impairment, adjustment of the recommended dose is not required, but patients should be monitored closely for adverse effects of colchicine. However, in patients with severe impairment, the starting dose should be 0.3 mg/day and any increase in dose should be done with close monitoring. For the prophylaxis of gout flares in patients undergoing dialysis, the starting doses should be 0.3 mg given twice a week with close monitoring [see *Clinical Pharmacology* (12.3) and *Renal Impairment* (8.6)].

#### **Treatment of Gout Flares**

For treatment of gout flares in patients with mild (Cl<sub>cr</sub> 50 to 80 mL/min) to moderate (Cl<sub>cr</sub> 30 to 50 mL/min) renal function impairment, adjustment of the recommended dose is not required, but patients should be monitored closely for adverse effects of colchicine. However, in patients with severe impairment, while the dose does not need to be adjusted for the treatment of gout flares, a treatment course should be repeated no more than once every two weeks. For patients with gout flares requiring repeated courses, consideration should be given to alternate therapy. For patients undergoing dialysis, the total recommended dose for the treatment of gout flares should be reduced to a single dose of 0.6 mg (one tablet). For these patients, the treatment course should not be repeated more than once every two weeks [see *Clinical Pharmacology* (12.3) and *Renal Impairment* (8.6)].

Treatment of gout flares with COLCRYS is not recommended in patients with renal impairment who are receiving COLCRYS for prophylaxis.

### **FMF**

Caution should be taken in dosing patients with moderate and severe renal impairment and in patients undergoing dialysis. For these patients, the dosage should be reduced [see *Clinical Pharmacology* (12.3)]. Patients with mild (Cl<sub>cr</sub> 50 to 80 mL/min) and moderate (Cl<sub>cr</sub> 30 to 50 mL/min) renal impairment should be monitored closely for adverse effects of COLCRYS. Dose reduction may be necessary. For patients with severe renal failure (Cl<sub>cr</sub> less than 30 mL/min), start with 0.3 mg/day; any increase in dose should be done with adequate monitoring of the patient for adverse effects of colchicine [see *Renal Impairment* (8.6)]. For patients undergoing dialysis, the total recommended starting dose should be 0.3 mg (half tablet) per day. Dosing can be increased with close monitoring. Any increase in dose should be done with adequate monitoring of the patient for adverse effects of colchicine [see *Clinical Pharmacology* (12.3) and *Renal Impairment* (8.6)].

## **2.6 Dose Modification in Hepatic Impairment**

### **Gout Flares**

#### ***Prophylaxis of Gout Flares***

For prophylaxis of gout flares in patients with mild to moderate hepatic function impairment, adjustment of the recommended dose is not required, but patients should be monitored closely for adverse effects of colchicine. Dose reduction should be considered for the prophylaxis of gout flares in patients with severe hepatic impairment [see *Hepatic Impairment (8.7)*].

#### ***Treatment of Gout Flares***

For treatment of gout flares in patients with mild to moderate hepatic function impairment, adjustment of the recommended dose is not required, but patients should be monitored closely for adverse effects of colchicine. However, for the treatment of gout flares in patients with severe impairment, while the dose does not need to be adjusted, a treatment course should be repeated no more than once every two weeks. For these patients, requiring repeated courses for the treatment of gout flares, consideration should be given to alternate therapy [see *Hepatic Impairment (8.7)*].

Treatment of gout flares with COLCRYS is not recommended in patients with hepatic impairment who are receiving COLCRYS for prophylaxis.

### **FMF**

Patients with mild to moderate hepatic impairment should be monitored closely for adverse effects of colchicine. Dose reduction should be considered in patients with severe hepatic impairment [see *Hepatic Impairment (8.7)*].

## **3 DOSAGE FORMS AND STRENGTHS**

0.6 mg tablets — purple capsule-shaped, film-coated with “AR 374” debossed on one side and scored on the other side.

## **4 CONTRAINDICATIONS**

Patients with renal or hepatic impairment should not be given COLCRYS in conjunction with P-gp or strong CYP3A4 inhibitors (this includes all protease inhibitors except fosamprenavir). In these patients, life-threatening and fatal colchicine toxicity has been reported with colchicine taken in therapeutic doses.

## **5 WARNINGS AND PRECAUTIONS**

### **5.1 Fatal Overdose**

Fatal overdoses, both accidental and intentional, have been reported in adults and children who have ingested colchicine [see *Overdosage (10)*]. COLCRYS should be kept out of the reach of children.

### **5.2 Blood Dyscrasias**

Myelosuppression, leukopenia, granulocytopenia, thrombocytopenia, pancytopenia and aplastic anemia have been reported with colchicine used in therapeutic doses.

### **5.3 Drug Interactions**

Colchicine is a P-gp and CYP3A4 substrate. Life-threatening and fatal drug interactions have been reported in patients treated with colchicine given with P-gp and strong CYP3A4 inhibitors. If treatment with a P-gp or strong CYP3A4 inhibitor is required in patients with normal renal and hepatic function, the patient's dose of colchicine may need to be reduced or interrupted [see *Drug Interactions (7)*]. Use of COLCRYS in

conjunction with P-gp or strong CYP3A4 inhibitors (this includes all protease inhibitors except fosamprenavir) is contraindicated in patients with renal or hepatic impairment [see *Contraindications* (4)].

#### **5.4 Neuromuscular Toxicity**

Colchicine-induced neuromuscular toxicity and rhabdomyolysis have been reported with chronic treatment in therapeutic doses. Patients with renal dysfunction and elderly patients, even those with normal renal and hepatic function, are at increased risk. Concomitant use of atorvastatin, simvastatin, pravastatin, fluvastatin, lovastatin, gemfibrozil, fenofibrate, fenofibric acid or benzaifibrate (themselves associated with myotoxicity) or cyclosporine with COLCRYS may potentiate the development of myopathy [see *Drug Interactions* (7)]. Once colchicine is stopped, the symptoms generally resolve within one week to several months.

### **6 ADVERSE REACTIONS**

#### **Prophylaxis of Gout Flares**

The most commonly reported adverse reaction in clinical trials of colchicine for the prophylaxis of gout was diarrhea.

#### **Treatment of Gout Flares**

The most common adverse reactions reported in the clinical trial with COLCRYS for treatment of gout flares were diarrhea (23%) and pharyngolaryngeal pain (3%).

#### **FMF**

Gastrointestinal tract adverse effects are the most frequent side effects in patients initiating COLCRYS, usually presenting within 24 hours, and occurring in up to 20% of patients given therapeutic doses. Typical symptoms include cramping, nausea, diarrhea, abdominal pain and vomiting. These events should be viewed as dose-limiting if severe, as they can herald the onset of more significant toxicity.

#### **6.1 Clinical Trials Experience in Gout**

Because clinical studies are conducted under widely varying and controlled conditions, adverse reaction rates observed in clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not predict the rates observed in a broader patient population in clinical practice.

In a randomized, double-blind, placebo-controlled trial in patients with a gout flare, gastrointestinal adverse reactions occurred in 26% of patients using the recommended dose (1.8 mg over one hour) of COLCRYS compared to 77% of patients taking a nonrecommended high dose (4.8 mg over six hours) of colchicine and 20% of patients taking placebo. Diarrhea was the most commonly reported drug-related gastrointestinal adverse event. As shown in Table 3, diarrhea is associated with COLCRYS treatment. Diarrhea was more likely to occur in patients taking the high-dose regimen than the low-dose regimen. Severe diarrhea occurred in 19% and vomiting occurred in 17% of patients taking the nonrecommended high-dose colchicine regimen but did not occur in the recommended low-dose COLCRYS regimen.

<b>Table 3. Number (%) of Patients with at Least One Drug-Related Treatment-Emergent Adverse Event with an Incidence of <math>\geq 2\%</math> of Patients in Any Treatment Group</b>			
<b>MedDRA System Organ Class MedDRA Preferred Term</b>	<b>COLCRYS Dose</b>		<b>Placebo (N=59) n (%)</b>
	<b>High (N=52) n (%)</b>	<b>Low (N=74) n (%)</b>	
Number of Patients with at Least One Drug-Related TEAE	40 (77)	27 (37)	16 (27)
Gastrointestinal Disorders	40 (77)	19 (26)	12 (20)
Diarrhea	40 (77)	17 (23)	8 (14)
Nausea	9 (17)	3 (4)	3 (5)
Vomiting	9 (17)	0	0
Abdominal Discomfort	0	0	2 (3)
General Disorders and Administration Site Conditions	4 (8)	1 (1)	1 (2)
Fatigue	2 (4)	1 (1)	1 (2)
Metabolic and Nutrition Disorders	0	3 (4)	2 (3)
Gout	0	3 (4)	1 (2)
Nervous System Disorders	1 (2)	1 (1.4)	2 (3)
Headache	1 (2)	1 (1)	2 (3)
Respiratory Thoracic Mediastinal Disorders	1 (2)	2 (3)	0
Pharyngolaryngeal Pain	1 (2)	2 (3)	0

## 6.2 Postmarketing Experience

Serious toxic manifestations associated with colchicine include myelosuppression, disseminated intravascular coagulation and injury to cells in the renal, hepatic, circulatory and central nervous systems.

These most often occur with excessive accumulation or overdosage [see *Overdosage (10)*].

The following adverse reactions have been reported with colchicine. These have been generally reversible upon temporarily interrupting treatment or lowering the dose of colchicine.

*Neurological:* sensory motor neuropathy

*Dermatological:* alopecia, maculopapular rash, purpura, rash

*Digestive:* abdominal cramping, abdominal pain, diarrhea, lactose intolerance, nausea, vomiting

*Hematological:* leukopenia, granulocytopenia, thrombocytopenia, pancytopenia, aplastic anemia

*Hepatobiliary:* elevated AST, elevated ALT

*Musculoskeletal:* myopathy, elevated CPK, myotonia, muscle weakness, muscle pain, rhabdomyolysis

*Reproductive:* azoospermia, oligospermia

## 7 DRUG INTERACTIONS

COLCRYS (colchicine) is a substrate of the efflux transporter P-glycoprotein (P-gp). Of the cytochrome P450 enzymes tested, CYP3A4 was mainly involved in the metabolism of colchicine. If COLCRYS is administered with drugs that inhibit P-gp, most of which also inhibit CYP3A4, increased concentrations of colchicine are likely. Fatal drug interactions have been reported.

Physicians should ensure that patients are suitable candidates for treatment with COLCRYS and remain alert for signs and symptoms of toxicities related to increased colchicine exposure as a result of a drug interaction. Signs and symptoms of COLCRYS toxicity should be evaluated promptly and, if toxicity is suspected, COLCRYS should be discontinued immediately.

Table 4 provides recommendations as a result of other potentially significant drug interactions. Table 1 provides recommendations for strong and moderate CYP3A4 inhibitors and P-gp inhibitors.

<b>Table 4. Other Potentially Significant Drug Interactions</b>		
<b>Concomitant Drug Class or Food</b>	<b>Noted or Anticipated Outcome</b>	<b>Clinical Comment</b>
<b>HMG-Co A Reductase Inhibitors:</b> atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin	Pharmacokinetic and/or pharmacodynamic interaction: the addition of one drug to a stable long-term regimen of the other has resulted in myopathy and rhabdomyolysis (including a fatality)	Weigh the potential benefits and risks and carefully monitor patients for any signs or symptoms of muscle pain, tenderness, or weakness, particularly during initial therapy; monitoring CPK (creatine phosphokinase) will not necessarily prevent the occurrence of severe myopathy.
<b>Other Lipid-Lowering Drugs:</b> fibrates, gemfibrozil		
<b>Digitalis Glycosides:</b> digoxin		

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Pregnancy Category C.

There are no adequate and well-controlled studies with colchicine in pregnant women. Colchicine crosses the human placenta. While not studied in the treatment of gout flares, data from a limited number of published studies found no evidence of an increased risk of miscarriage, stillbirth or teratogenic effects among pregnant women using colchicine to treat familial Mediterranean fever (FMF). Although animal reproductive and developmental studies were not conducted with COLCRYS, published animal reproduction and development studies indicate that colchicine causes embryofetal toxicity, teratogenicity and altered postnatal development at exposures within or above the clinical therapeutic range. COLCRYS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

### 8.2 Labor and Delivery

The effect of colchicine on labor and delivery is unknown.

### 8.3 Nursing Mothers

Colchicine is excreted into human milk. Limited information suggests that exclusively breastfed infants receive less than 10 percent of the maternal weight-adjusted dose. While there are no published reports of adverse effects in breastfeeding infants of mothers taking colchicine, colchicine can affect gastrointestinal cell renewal and permeability. Caution should be exercised, and breastfeeding infants should be observed for adverse effects when COLCRYS is administered to a nursing woman.

### 8.4 Pediatric Use

The safety and efficacy of colchicine in children of all ages with FMF has been evaluated in uncontrolled studies. There does not appear to be an adverse effect on growth in children with FMF treated long-term with colchicine. Gout is rare in pediatric patients; safety and effectiveness of colchicine in pediatric patients has not been established.

## 8.5 Geriatric Use

Clinical studies with colchicine for prophylaxis and treatment of gout flares and for treatment of FMF did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient with gout should be cautious, reflecting the greater frequency of decreased renal function, concomitant disease or other drug therapy [see *Dose Modification for Coadministration of Interacting Drugs (2.4) and Pharmacokinetics (12.3)*].

## 8.6 Renal Impairment

Colchicine is significantly excreted in urine in healthy subjects. Clearance of colchicine is decreased in patients with impaired renal function. Total body clearance of colchicine was reduced by 75% in patients with end-stage renal disease undergoing dialysis.

### Prophylaxis of Gout Flares

For prophylaxis of gout flares in patients with mild (estimated creatinine clearance  $Cl_{cr}$  50 to 80 mL/min) to moderate ( $Cl_{cr}$  30 to 50 mL/min) renal function impairment, adjustment of the recommended dose is not required, but patients should be monitored closely for adverse effects of colchicine. However, in patients with severe impairment, the starting dose should be 0.3 mg per day and any increase in dose should be done with close monitoring. For the prophylaxis of gout flares in patients undergoing dialysis, the starting doses should be 0.3 mg given twice a week with close monitoring [see *Dose Modification in Renal Impairment (2.5)*].

### Treatment of Gout Flares

For treatment of gout flares in patients with mild ( $Cl_{cr}$  50 to 80 mL/min) to moderate ( $Cl_{cr}$  30 to 50 mL/min) renal function impairment, adjustment of the recommended dose is not required, but patients should be monitored closely for adverse effects of COLCRYS. However, in patients with severe impairment, while the dose does not need to be adjusted for the treatment of gout flares, a treatment course should be repeated no more than once every two weeks. For patients with gout flares requiring repeated courses, consideration should be given to alternate therapy. For patients undergoing dialysis, the total recommended dose for the treatment of gout flares should be reduced to a single dose of 0.6 mg (one tablet). For these patients, the treatment course should not be repeated more than once every two weeks [see *Dose Modification in Renal Impairment (2.5)*].

## FMF

Although, pharmacokinetics of colchicine in patients with mild ( $Cl_{cr}$  50 to 80 mL/min) and moderate ( $Cl_{cr}$  30 to 50 mL/min) renal impairment is not known, these patients should be monitored closely for adverse effects of colchicine. Dose reduction may be necessary. In patients with severe renal failure ( $Cl_{cr}$  less than 30 mL/min) and end-stage renal disease requiring dialysis, COLCRYS may be started at the dose of 0.3 mg/day. Any increase in dose should be done with adequate monitoring of the patient for adverse effects of COLCRYS [see *Pharmacokinetics (12.3) and Dose Modification in Renal Impairment (2.5)*].

## 8.7 Hepatic Impairment

The clearance of colchicine may be significantly reduced and plasma half-life prolonged in patients with chronic hepatic impairment compared to healthy subjects [see *Pharmacokinetics (12.3)*].

**Prophylaxis of Gout Flares**

For prophylaxis of gout flares in patients with mild to moderate hepatic function impairment, adjustment of the recommended dose is not required, but patients should be monitored closely for adverse effects of colchicine. Dose reduction should be considered for the prophylaxis of gout flares in patients with severe hepatic impairment [see *Dose Modification in Hepatic Impairment* (2.6)].

**Treatment of Gout Flares**

For treatment of gout flares in patients with mild to moderate hepatic function impairment, adjustment of the recommended COLCRYS dose is not required, but patients should be monitored closely for adverse effects of COLCRYS. However, for the treatment of gout flares in patients with severe impairment, while the dose does not need to be adjusted, the treatment course should be repeated no more than once every two weeks. For these patients, requiring repeated courses for the treatment of gout flares, consideration should be given to alternate therapy [see *Dose Modification in Hepatic Impairment* (2.6)].

**FMF**

In patients with severe hepatic disease, dose reduction should be considered with careful monitoring [see *Pharmacokinetics* (12.3) and *Dose Modification in Hepatic Impairment* (2.6)].

**9 DRUG ABUSE AND DEPENDENCE**

Tolerance, abuse or dependence with colchicine has not been reported.

**10 OVERDOSAGE**

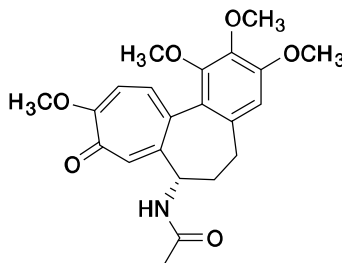
The exact dose of colchicine that produces significant toxicity is unknown. Fatalities have occurred after ingestion of a dose as low as 7 mg over a four-day period, while other patients have survived after ingesting more than 60 mg. A review of 150 patients who overdosed on colchicine found that those who ingested less than 0.5 mg/kg survived and tended to have milder toxicities such as gastrointestinal symptoms, whereas those who took 0.5 to 0.8 mg/kg had more severe reactions such as myelosuppression. There was 100% mortality in those who ingested more than 0.8 mg/kg.

The first stage of acute colchicine toxicity typically begins within 24 hours of ingestion and includes gastrointestinal symptoms such as abdominal pain, nausea, vomiting, diarrhea and significant fluid loss, leading to volume depletion. Peripheral leukocytosis may also be seen. Life-threatening complications occur during the second stage, which occurs 24 to 72 hours after drug administration, attributed to multiorgan failure and its consequences. Death is usually a result of respiratory depression and cardiovascular collapse. If the patient survives, recovery of multiorgan injury may be accompanied by rebound leukocytosis and alopecia starting about one week after the initial ingestion.

Treatment of colchicine poisoning should begin with gastric lavage and measures to prevent shock. Otherwise, treatment is symptomatic and supportive. No specific antidote is known. Colchicine is not effectively removed by dialysis [see *Pharmacokinetics* (12.3)].

## 11 DESCRIPTION

Colchicine is an alkaloid chemically described as (S)-N- (5,6,7,9-tetrahydro- 1,2,3, 10-tetramethoxy-9-oxobenzo [alpha] heptalen-7-yl) acetamide with a molecular formula of  $C_{22}H_{25}NO_6$  and a molecular weight of 399.4. The structural formula of colchicine is given below.



Colchicine occurs as a pale yellow powder that is soluble in water.

COLCRYS (colchicine, USP) tablets are supplied for oral administration as purple, film-coated, capsule-shaped tablets (0.1575" × 0.3030"), debossed with "AR 374" on one side and scored on the other, containing 0.6 mg of the active ingredient colchicine USP. Inactive ingredients: carnauba wax, FD&C blue #2, FD&C red #40, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polydextrose, polyethylene glycol, pregelatinized starch, sodium starch glycolate, titanium dioxide and triacetin.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

The mechanism by which COLCRYS exerts its beneficial effect in patients with FMF has not been fully elucidated; however, evidence suggests that colchicine may interfere with the intracellular assembly of the inflammasome complex present in neutrophils and monocytes that mediates activation of interleukin-1 $\beta$ . Additionally, colchicine disrupts cytoskeletal functions through inhibition of  $\beta$ -tubulin polymerization into microtubules and consequently prevents the activation, degranulation and migration of neutrophils thought to mediate some gout symptoms.

### 12.3 Pharmacokinetics

#### Absorption

In healthy adults, COLCRYS is absorbed when given orally, reaching a mean  $C_{max}$  of 2.5 ng/mL (range 1.1 to 4.4 ng/mL) in one to two hours (range 0.5 to three hours) after a single dose administered under fasting conditions.

Following oral administration of COLCRYS given as 1.8 mg colchicine over one hour to healthy, young adults under fasting conditions, colchicine appears to be readily absorbed, reaching mean maximum plasma concentrations of 6.2 ng/mL at a median 1.81 hours (range: 1.0 to 2.5 hours). Following administration of the nonrecommended high-dose regimen (4.8 mg over six hours), mean maximal plasma concentrations were 6.8 ng/mL, at a median 4.47 hours (range: 3.1 to 7.5 hours).

After 10 days on a regimen of 0.6 mg twice daily, peak concentrations are 3.1 to 3.6 ng/mL (range 1.6 to 6.0 ng/mL), occurring 1.3 to 1.4 hours postdose (range 0.5 to 3.0 hours). Mean pharmacokinetic parameter values in healthy adults are shown in Table 5.

Table 5. Mean (%CV) Pharmacokinetic Parameters in Healthy Adults Given COLCRYS				
C <sub>max</sub> (Colchicine ng/mL)	T <sub>max</sub> * (h)	Vd/F (L)	CL/F (L/hr)	t <sub>1/2</sub> (h)
COLCRYS 0.6 mg Single Dose (N=13)				
2.5 (28.7)	1.5 (1.0 – 3.0)	341.5 (54.4)	54.1 (31.0)	--
COLCRYS 0.6 mg Twice Daily x 10 Days (N=13)				
3.6 (23.7)	1.3 (0.5 – 3.0)	1150 (18.7)	30.3 (19.0)	26.6 (16.3)

\*T<sub>max</sub> mean (range)CL = Dose/AUC<sub>0-t</sub> (calculated from mean values)

Vd = CL/Ke (calculated from mean values)

In some subjects, secondary colchicine peaks are seen, occurring between three and 36 hours postdose and ranging from 39% to 155% of the height of the initial peak. These observations are attributed to intestinal secretion and reabsorption and/or biliary recirculation.

Absolute bioavailability is reported to be approximately 45%.

Administration of COLCRYS with food has no effect on the rate of colchicine absorption but does decrease the extent of colchicine by approximately 15%. This is without clinical significance.

### Distribution

The mean apparent volume of distribution in healthy young volunteers is approximately 5 to 8 L/kg.

Colchicine binding to serum protein is low, 39 ± 5%, primarily to albumin regardless of concentration.

Colchicine crosses the placenta (plasma levels in the fetus are reported to be approximately 15% of the maternal concentration). Colchicine also distributes into breast milk at concentrations similar to those found in the maternal serum [see *Pregnancy (8.1) and Nursing Mothers (8.3)*].

### Metabolism

Colchicine is demethylated to two primary metabolites, 2-O-demethylcolchicine and 3-O-demethylcolchicine (2- and 3-DMC, respectively) and one minor metabolite, 10-O-demethylcolchicine (also known as colchiceine). *In vitro* studies using human liver microsomes have shown that CYP3A4 is involved in the metabolism of colchicine to 2- and 3-DMC. Plasma levels of these metabolites are minimal (less than 5% of parent drug).

### Elimination/Excretion

In healthy volunteers (n=12), 40% to 65% of 1 mg orally administered colchicine was recovered unchanged in urine. Enterohepatic recirculation and biliary excretion are also postulated to play a role in colchicine elimination. Following multiple oral doses (0.6 mg twice daily), the mean elimination half-lives in young healthy volunteers (mean age 25 to 28 years of age) is 26.6 to 31.2 hours. Colchicine is a substrate of P-gp.

### Extracorporeal Elimination

Colchicine is not removed by hemodialysis.

**Special Populations**

There is no difference between men and women in the pharmacokinetic disposition of colchicine.

**Pediatric Patients:** Pharmacokinetics of colchicine was not evaluated in pediatric patients.

**Elderly:** A published report described the pharmacokinetics of 1 mg oral colchicine tablet in four elderly women compared to six young healthy males. The mean age of the four elderly women was 83 years (range 75 to 93), mean weight was 47 kg (38 to 61 kg) and mean creatinine clearance was 46 mL/min (range 25 to 75 mL/min). Mean peak plasma levels and AUC of colchicine were two times higher in elderly subjects compared to young healthy males.

A pharmacokinetic study using a single oral dose of one 0.6 mg colchicine tablet was conducted in young healthy subjects (n=20) between the ages of 18 and 30 years and elderly subjects (n=18) between the ages of 60 and 70 years. Elderly subjects in this study had a median age of 62 years and a mean ( $\pm$ SD) age of  $62.83 \pm 2.83$  years. A statistically significant difference in creatinine clearance (mean  $\pm$  SD) was found between the two age groups ( $132.56 \pm 23.16$  mL/min for young vs.  $87.02 \pm 17.92$  mL/min for elderly subjects, respectively). The following pharmacokinetic parameter values (mean  $\pm$  SD) were observed for colchicine in the young and elderly subjects, respectively:  $AUC_{0-\infty}$  (ng/hr/mL)  $22.39 \pm 6.95$  and  $25.01 \pm 6.92$ ;  $C_{max}$  (ng/mL)  $2.61 \pm 0.71$  and  $2.56 \pm 0.97$ ;  $T_{max}$  (hr)  $1.38 \pm 0.42$  and  $1.25 \pm 0.43$ ; apparent elimination half-life (hr)  $24.92 \pm 5.34$  and  $30.06 \pm 10.78$ ; and clearance (mL/min)  $0.0321 \pm 0.0091$  and  $0.0292 \pm 0.0071$ .

Clinical studies with colchicine for prophylaxis and treatment of gout flares and for treatment of FMF did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently than younger patients. In general, dose selection for an elderly patient with gout should be cautious, reflecting the greater frequency of decreased renal function, concomitant disease or other drug therapy [see *Dose Modification for Coadministration of Interacting Drugs (2.4) and Geriatric Use (8.5)*].

**Renal Impairment:** Pharmacokinetics of colchicine in patients with mild and moderate renal impairment is not known. A published report described the disposition of colchicine (1 mg) in young adult men and women with FMF who had normal renal function or end-stage renal disease requiring dialysis. Patients with end-stage renal disease had 75% lower colchicine clearance (0.17 vs. 0.73 L/hr/kg) and prolonged plasma elimination half-life (18.8 hours vs. 4.4 hours) as compared to subjects with FMF and normal renal function [see *Dose Modification in Renal Impairment (2.5) and Renal Impairment (8.6)*].

**Hepatic Impairment:** Published reports on the pharmacokinetics of IV colchicine in patients with severe chronic liver disease, as well as those with alcoholic or primary biliary cirrhosis and normal renal function suggest wide interpatient variability. In some subjects with mild to moderate cirrhosis, the clearance of colchicine is significantly reduced and plasma half-life prolonged compared to healthy subjects. In subjects with primary biliary cirrhosis, no consistent trends were noted [see *Dose Modification in Hepatic Impairment (2.6) and Hepatic Impairment (8.7)*]. No pharmacokinetic data are available for patients with severe hepatic impairment (Child-Pugh C).

**Drug Interactions**

**In Vitro Drug Interactions:** *In vitro* studies in human liver microsomes have shown that colchicine is not an inhibitor or inducer of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4 activity.

**In Vivo Drug Interactions:** The effects of coadministration of other drugs with COLCRYS on  $C_{max}$ , AUC and  $C_{min}$  are summarized in Table 6 (effect of other drugs on colchicine) and Table 7 (effect of colchicine on other drugs). For information regarding clinical recommendations, see [Table 1](#) in Dose Modification for Coadministration of Interacting Drugs [see *Dose Modification for Coadministration of Interacting Drugs* (2.4)].

<b>Table 6. Drug Interactions: Pharmacokinetic Parameters for COLCRYS (Colchicine, USP) Tablets in the Presence of the Coadministered Drug</b>					
<b>Coadministered Drug</b>	<b>Dose of Coadministered Drug (mg)</b>	<b>Dose of COLCRYS (mg)</b>	<b>N</b>	<b>% Change in Colchicine Concentrations from Baseline (Range: Min - Max)</b>	
				<b><math>C_{max}</math></b>	<b>AUC<sub>0-t</sub></b>
Cyclosporine	100 mg single dose	0.6 mg single dose	23	270.0 (62.0 to 606.9)	259.0 (75.8 to 511.9)
Clarithromycin	250 mg twice daily, 7 days	0.6 mg single dose	23	227.2 (65.7 to 591.1)	281.5 (88.7 to 851.6)
Ketoconazole	200 mg twice daily, 5 days	0.6 mg single dose	24	101.7 (19.6 to 219.0)	212.2 (76.7 to 419.6)
Ritonavir	100 mg twice daily, 5 days	0.6 mg single dose	18	184.4 (79.2 to 447.4)	296.0 (53.8 to 924.4)
Verapamil	240 mg daily, 5 days	0.6 mg single dose	24	40.1 (-47.1 to 149.5)	103.3 (-9.8 to 217.2)
Diltiazem	240 mg daily, 7 days	0.6 mg single dose	20	44.2 (-46.0 to 318.3)	93.4 (-30.2 to 338.6)
Azithromycin	500 mg × 1 day, then 250 mg × 4 days	0.6 mg single dose	21	21.6 (-41.7 to 222.0)	57.1 (-24.3 to 241.1)
Grapefruit juice	240 mL twice daily, 4 days	0.6 mg single dose	21	-2.55 (-53.4 to 55.0)	-2.36 (-46.4 to 62.2)

Estrogen-containing oral contraceptives: In healthy female volunteers given ethinyl estradiol and norethindrone (Ortho-Novum 1/35) coadministered with COLCRYS (0.6 mg twice daily × 14 days), hormone concentrations are not affected.

In healthy volunteers given theophylline coadministered with COLCRYS (0.6 mg twice daily × 14 days), theophylline concentrations were not affected.

<b>Table 7. Drug Interactions: Pharmacokinetic Parameters for Coadministration of Drug in the Presence of COLCRYS (Colchicine, USP) Tablets</b>					
<b>Coadministered Drug</b>	<b>Dose of Coadministered Drug (mg)</b>	<b>Dose of COLCRYS (mg)</b>	<b>N</b>	<b>% Change in Coadministered Drug Concentrations from Baseline (Range: Min - Max)</b>	
				<b>C<sub>max</sub></b>	<b>AUC<sub>0-t</sub></b>
Theophylline	300 mg (elixir) single dose	0.6 mg twice daily × 14 days	27	1.6 (-30.4 to 23.1)	1.6 (-28.5 to 27.1)
Ethinyl Estradiol (Ortho-Novum 1/35)	21-day cycle (active treatment) + 7-day placebo	0.6 mg twice daily × 14 days	27*	-6.7 (-40.3 to 44.7)	-3.0 <sup>†</sup> (-25.3 to 24.9)
Norethindrone (Ortho-Novum 1/35)				0.94 (-37.3 to 59.4)	-1.6 <sup>†</sup> (-32.0 to 33.7)

\*Conducted in healthy adult females

<sup>†</sup>AUC<sub>τ</sub>

### 13 NONCLINICAL TOXICOLOGY

#### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

##### Carcinogenesis

Carcinogenicity studies of colchicine have not been conducted. Due to the potential for colchicine to produce aneuploid cells (cells with an unequal number of chromosomes), there is theoretically an increased risk of malignancy.

##### Mutagenesis

Colchicine was negative for mutagenicity in the bacterial reverse mutation assay. In a chromosomal aberration assay in cultured human white blood cells, colchicine treatment resulted in the formation of micronuclei. Since published studies demonstrated that colchicine induces aneuploidy from the process of mitotic nondisjunction without structural DNA changes, colchicine is not considered clastogenic, although micronuclei are formed.

##### Impairment of Fertility

No studies of colchicine effects on fertility were conducted with COLCRYS. However, published nonclinical studies demonstrated that colchicine-induced disruption of microtubule formation affects meiosis and mitosis. Reproductive studies also reported abnormal sperm morphology and reduced sperm counts in males, and interference with sperm penetration, second meiotic division and normal cleavage in females when exposed to colchicine. Colchicine administered to pregnant animals resulted in fetal death and teratogenicity. These effects were dose-dependent, with the timing of exposure critical for the effects on embryofetal development. The nonclinical doses evaluated were generally higher than an equivalent human therapeutic dose, but safety margins for reproductive and developmental toxicity could not be determined.

Case reports and epidemiology studies in human male subjects on colchicine therapy indicated that infertility from colchicine is rare. A case report indicated that azoospermia was reversed when therapy was stopped. Case reports and epidemiology studies in female subjects on colchicine therapy have not established a clear relationship between colchicine use and female infertility. However, since the progression of FMF without treatment may result in infertility, the use of colchicine needs to be weighed against the potential risks.

## 14 CLINICAL STUDIES

The evidence for the efficacy of colchicine in patients with chronic gout is derived from the published literature. Two randomized clinical trials assessed the efficacy of colchicine 0.6 mg twice a day for the prophylaxis of gout flares in patients with gout initiating treatment with urate-lowering therapy. In both trials, treatment with colchicine decreased the frequency of gout flares.

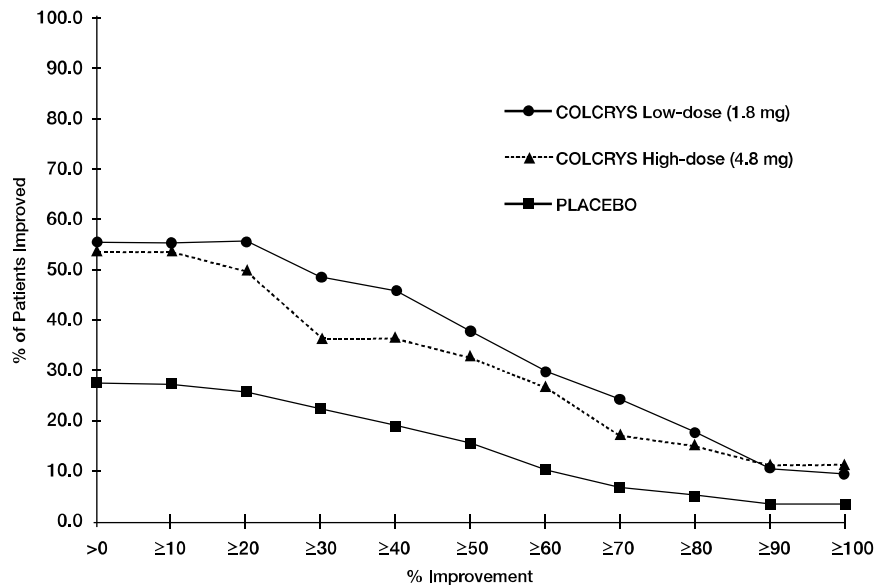
The efficacy of a low-dosage regimen of oral colchicine (COLCRYS total dose 1.8 mg over one hour) for treatment of gout flares was assessed in a multicenter, randomized, double-blind, placebo-controlled, parallel group, one-week, dose-comparison study. Patients meeting American College of Rheumatology criteria for gout were randomly assigned to three groups: high-dose colchicine (1.2 mg, then 0.6 mg hourly × 6 hours [4.8 mg total]); low-dose colchicine (1.2 mg, then 0.6 mg in 1 hour [1.8 mg total] followed by five placebo doses hourly); or placebo (two capsules, then one capsule hourly × 6 hours). Patients took the first dose within 12 hours of the onset of the flare and recorded pain intensity (11-point Likert scale) and adverse events over 72 hours. The efficacy of colchicine was measured based on response to treatment in the target joint, using patient self-assessment of pain at 24 hours following the time of first dose as recorded in the diary. A responder was one who achieved at least a 50% reduction in pain score at the 24-hour postdose assessment relative to the pretreatment score and did not use rescue medication prior to the actual time of 24-hour postdose assessment.

Rates of response were similar for the recommended low-dose treatment group (38%) and the nonrecommended high-dose group (33%) but were higher as compared to the placebo group (16%) as shown in Table 8.

<b>Table 8. Number (%) of Responders Based on Target Joint Pain Score at 24 Hours Post First Dose</b>				
<b>COLCRYS Dose Responders n (%)</b>		<b>Placebo n (%)</b>	<b>% Differences in Proportion</b>	
<b>Low-Dose (n=74)</b>	<b>High-Dose (n=52)</b>		<b>Low-Dose vs Placebo (95% CI)</b>	<b>High-Dose vs Placebo (95% CI)</b>
28 (38%)	17 (33%)	9 (16%)	22 (8, 37)	17 (1, 33)

Figure 1 shows the percentage of patients achieving varying degrees of improvement in pain from baseline at 24 hours.

**Figure 1**  
**Pain Relief on Low and High Doses of COLCRYS and Placebo (Cumulative)**



The evidence for the efficacy of colchicine in patients with FMF is derived from the published literature. Three randomized, placebo-controlled studies were identified. The three placebo-controlled studies randomized a total of 48 adult patients diagnosed with FMF and reported similar efficacy endpoints as well as inclusion and exclusion criteria.

One of the studies randomized 15 patients with FMF to a six-month crossover study during which five patients discontinued due to study noncompliance. The 10 patients completing the study experienced five attacks over the course of 90 days while treated with colchicine compared to 59 attacks over the course of 90 days while treated with placebo. Similarly, the second study randomized 22 patients with FMF to a four-month crossover study during which nine patients discontinued due to lack of efficacy while receiving placebo or study noncompliance. The 13 patients completing the study experienced 18 attacks over the course of 60 days while treated with colchicine compared to 68 attacks over the course of 60 days while treated with placebo. The third study was discontinued after an interim analysis of six of the 11 patients enrolled had completed the study; results could not be confirmed.

Open-label experience with colchicine in adults and children with FMF is consistent with the randomized, controlled trial experience and was utilized to support information on the safety profile of colchicine and for dosing recommendations.

## **16 HOW SUPPLIED/STORAGE AND HANDLING**

### **16.1 How Supplied**

COLCRYS (colchicine, USP) tablets 0.6 mg are purple, film-coated, capsule-shaped tablets debossed with "AR 374" on one side and scored on the other side.

Bottles of 30	NDC 64764-119-07
Bottles of 60	NDC 64764-119-06
Bottles of 100	NDC 64764-119-01
Bottles of 250	NDC 64764-119-03
Bottles of 500	NDC 64764-119-05

Bottles of 1000

NDC 64764-119-10

## **16.2 Storage**

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Protect from light.

DISPENSE IN TIGHT, LIGHT-RESISTANT CONTAINER.

## **17 PATIENT COUNSELING INFORMATION**

See [FDA-approved Medication Guide](#).

### **17.1 Dosing Instructions**

Patients should be advised to take COLCRYS as prescribed, even if they are feeling better. Patients should not alter the dose or discontinue treatment without consulting with their doctor. If a dose of COLCRYS is missed:

- For treatment of a gout flare when the patient is not being dosed for prophylaxis, take the missed dose as soon as possible.
- For treatment of a gout flare during prophylaxis, take the missed dose immediately, wait 12 hours, then resume the previous dosing schedule.
- For prophylaxis without treatment for a gout flare, or FMF, take the dose as soon as possible and then return to the normal dosing schedule. However, if a dose is skipped the patient should not double the next dose.

### **17.2 Fatal Overdose**

Instruct patient that fatal overdoses, both accidental and intentional, have been reported in adults and children who have ingested colchicine. COLCRYS should be kept out of the reach of children.

### **17.3 Blood Dyscrasias**

Patients should be informed that bone marrow depression with agranulocytosis, aplastic anemia and thrombocytopenia may occur with COLCRYS.

### **17.4 Drug and Food Interactions**

Patients should be advised that many drugs or other substances may interact with COLCRYS and some interactions could be fatal. Therefore, patients should report to their healthcare provider all of the current medications they are taking and check with their healthcare provider before starting any new medications, particularly antibiotics. Patients should also be advised to report the use of nonprescription medication or herbal products. Grapefruit and grapefruit juice may also interact and should not be consumed during COLCRYS treatment.

### **17.5 Neuromuscular Toxicity**

Patients should be informed that muscle pain or weakness, tingling or numbness in fingers or toes may occur with COLCRYS alone or when it is used with certain other drugs. Patients developing any of these signs or symptoms must discontinue COLCRYS and seek medical evaluation immediately.

**MEDICATION GUIDE****COLCRYS (KOL-kris)  
(colchicine) tablets**

Read the Medication Guide that comes with COLCRYS before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or treatment. You and your healthcare provider should talk about COLCRYS when you start taking it and at regular checkups.

**What is the most important information that I should know about COLCRYS?**

COLCRYS can cause serious side effects or death if levels of COLCRYS are too high in your body.

- Taking certain medicines with COLCRYS can cause your level of COLCRYS to be too high, especially if you have kidney or liver problems.
- Tell your healthcare provider about all your medical conditions, including if you have kidney or liver problems. Your dose of COLCRYS may need to be changed.
- Tell your healthcare provider about all the medicines you take, including prescription and nonprescription medicines, vitamins and herbal supplements.
- Even medicines that you take for a short period of time, such as antibiotics, can interact with COLCRYS and cause serious side effects or death.
- Talk to your healthcare provider or pharmacist before taking any new medicine.
- Especially tell your healthcare provider if you take:
 

• atazanavir sulfate (Reyataz)	• clarithromycin (Biaxin)
• cyclosporine (Neoral, Gengraf, Sandimmune)	• darunavir (Prezista)
• fosamprenavir (Lexiva) with ritonavir	• fosamprenavir (Lexiva)
• indinavir (Crixivan)	• itraconazole (Sporanox)
• ketoconazole (Nizoral)	• lopinavir/ritonavir (Kaletra)
• nefazodone (Serzone)	• nelfinavir mesylate (Viracept)
• ritonavir (Norvir)	• saquinavir mesylate (Invirase)
• telithromycin (Ketek)	• tipranavir (Aptivus)

Ask your healthcare provider or pharmacist if you are not sure if you take any of the medicines listed above. This is not a complete list of all the medicines that can interact with COLCRYS.

- Know the medicines you take. Keep a list of them and show it to your healthcare provider and pharmacist when you get a new medicine.
- Keep COLCRYS out of the reach of children.

**What is COLCRYS?**

COLCRYS is a prescription medicine used to:

- prevent and treat gout flares in adults
- treat familial Mediterranean fever (FMF) in adults and children age 4 or older

COLCRYS is not a pain medicine, and it should not be taken to treat pain related to other conditions unless specifically prescribed for those conditions.

**Who should not take COLCRYS?**

Do not take COLCRYS if you have liver or kidney problems and you take certain other medicines. Serious side effects, including death, have been reported in these patients even

when taken as directed. See **“What is the most important information that I should know about COLCRYS?”**

### **What should I tell my healthcare provider before starting COLCRYS?**

See **“What is the most important information that I should know about COLCRYS?”**

Before you take COLCRYS, tell your healthcare provider about all your medical conditions, including if you:

- have liver or kidney problems.
- are pregnant or plan to become pregnant. It is not known if COLCRYS will harm your unborn baby. Talk to your healthcare provider if you are pregnant or plan to become pregnant.
- are breastfeeding or plan to breastfeed. COLCRYS passes into your breast milk. You and your healthcare provider should decide if you will take COLCRYS or breastfeed. If you take COLCRYS and breastfeed, you should talk to your child’s healthcare provider about how to watch for side effects in your child.

Tell your healthcare provider about all the medicines you take, including ones that you may only be taking for a short time, such as antibiotics. See **“What is the most important information that I should know about COLCRYS?”** Do not start a new medicine without talking to your healthcare provider.

Using COLCRYS with certain other medicines, such as cholesterol-lowering medications and digoxin, can affect each other, causing serious side effects. Your healthcare provider may need to change your dose of COLCRYS. Talk to your healthcare provider about whether the medications you are taking might interact with COLCRYS and what side effects to look for.

### **How should I take COLCRYS?**

- Take COLCRYS exactly as your healthcare provider tells you to take it. **If you are not sure about your dosing**, call your healthcare provider.
- COLCRYS can be taken with or without food.
- If you take too much COLCRYS, go to the nearest hospital emergency room right away.
- Do not stop taking COLCRYS even if you start to feel better, unless your healthcare provider tells you.
- Your healthcare provider may do blood tests while you take COLCRYS.
- If you take COLCRYS daily and you miss a dose, then take it as soon as you remember. If it is almost time for your next dose, just skip the missed dose. Take the next dose at your regular time. Do not take two doses at the same time.
- If you have a gout flare while taking COLCRYS daily, report this to your healthcare provider.

### **What should I avoid while taking COLCRYS?**

- Avoid eating grapefruit or drinking grapefruit juice while taking COLCRYS. It can increase your chances of getting serious side effects.

### **What are the possible side effects of COLCRYS?**

COLCRYS can cause serious side effects or even cause death. See **“What is the most important information that I should know about COLCRYS?”**

Get medical help right away if you have:

- Muscle weakness or pain
- Numbness or tingling in your fingers or toes

- Unusual bleeding or bruising
- Increased infections
- Feel weak or tired
- Pale or gray color to your lips, tongue or palms of your hands
- Severe diarrhea or vomiting

**Gout Flares:** The most common side effect of COLCRYS in people who have gout flares is diarrhea.

**FMF:** The most common side effects of COLCRYS in people who have FMF are abdominal pain, diarrhea, nausea and vomiting.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all of the possible side effects of COLCRYS. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

#### **How should I store COLCRYS?**

- Store COLCRYS at room temperature between 68°F and 77°F (20°C and 25°C).
- Keep COLCRYS in a tightly closed container.
- Keep COLCRYS out of the light.

**Keep COLCRYS and all medicines out of the reach of children.**

#### **General Information about COLCRYS**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use COLCRYS for a condition for which it was not prescribed. Do not give COLCRYS to other people, even if they have the same symptoms that you have. It may harm them. This Medication Guide summarizes the most important information about COLCRYS. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about COLCRYS that is written for healthcare professionals.

For more information, go to [www.COLCRYS.com](http://www.COLCRYS.com) or call 1-877-825-3327.

#### **What are the ingredients in COLCRYS?**

**Active Ingredient:** colchicine.

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COL243 R1

# EXHIBIT B

# 2012 American College of Rheumatology Guidelines for Management of Gout. Part 2: Therapy and Antiinflammatory Prophylaxis of Acute Gouty Arthritis

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## Introduction

In response to a request for proposal from the American College of Rheumatology (ACR), our group was charged with developing nonpharmacologic and pharmacologic guidelines for treatments in gout that are safe and effective, i.e., with an acceptable risk/benefit ratio. These guidelines

for the management and antiinflammatory prophylaxis of acute attacks of gouty arthritis complement our article on

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## Significance & Innovations

- An acute gouty arthritis attack should be treated with pharmacologic therapy, initiated within 24 hours of onset.
- Established pharmacologic urate-lowering therapy should be continued, without interruption, during an acute attack of gout.
- Nonsteroidal antiinflammatory drugs (NSAIDs), corticosteroids, or oral colchicine are appropriate first-line options for treatment of acute gout, and certain combinations can be employed for severe or refractory attacks.
- Pharmacologic antiinflammatory prophylaxis is recommended for all gout patients when pharmacologic urate lowering is initiated, and should be continued if there is any clinical evidence of continuing gout disease activity and/or the serum urate target has not yet been achieved.
- Oral colchicine is an appropriate first-line gout attack prophylaxis therapy, including with appropriate dose adjustment in chronic kidney disease and for drug interactions, unless there is a lack of tolerance or medical contraindication.
- Low-dose NSAID therapy is an appropriate choice for first-line gout attack prophylaxis, unless there is a lack of tolerance or medical contraindication.

guidelines to treat hyperuricemia in patients with evidence of gout (or gouty arthritis) (1).

Gout is the most common cause of inflammatory arthritis in adults in the US. Clinical manifestations in joints and bursa are superimposed on local tissue deposition of monosodium urate crystals. Acute gout characteristically presents as a self-limited attack of synovitis (also called “gout flare”). Acute gout attacks account for a major component of the reported decreased health-related quality of life in patients with gout (2,3). Acute gout attacks can be debilitating and are associated with decreased work productivity (4,5).

Urate-lowering therapy (ULT) is a cornerstone in the management of gout (1) and, when effective in lowering serum urate, is associated with a decreased risk of acute gouty attacks (6). However, during the initial phase of ULT, there is an early increase in acute gout attacks, which has been hypothesized due to remodeling of articular urate crystal deposits as a result of rapid and substantial lowering of ambient urate concentrations (7). Acute gout attacks attributable to the initiation of ULT may contribute to nonadherence in long-term gout treatment, as reported in recent studies (8).

In order to systematically evaluate management of acute gouty arthritis, we generated multifaceted case scenarios to elucidate decision making based primarily on clinical and laboratory test-based data that can be obtained from a gout patient by both nonspecialist and specialist health care providers in an office practice setting. This effort was not intended to create a novel classification system of gout or new gout diagnostic criteria, since such endeavors are beyond the scope of this work.

Prior gout recommendations and guidelines, at the independent (i.e., non-pharmaceutical industry sponsored) national or multinational rheumatology society level, have

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been published by the European League Against Rheumatism (EULAR) (9,10), the Dutch College of General Practitioners (11), and the British Society for Rheumatology (BSR) (12). The ACR requested new guidelines in view of the increasing prevalence of gout (13), the clinical complexity of management of gouty arthritis imposed by comorbidities common in patients with gout (14), and increasing numbers of treatment options via clinical development of agents (15–17). The ACR charged us to develop these guidelines to be useful for both rheumatologists and other health care providers on an international level. As such, this process and resultant recommendations involved a diverse and international panel of experts.

In this article, we concentrate on 2 of the 4 gout domains (1) that the ACR requested for evaluation of pharmacologic and nonpharmacologic management approaches: analgesic and antiinflammatory management of acute attacks of gouty arthritis and pharmacologic antiinflammatory prophylaxis of acute attacks of gouty arthritis. Part 1 of the guidelines focused on systematic nonpharmacologic measures (patient education, diet and lifestyle choices, identification and management of comorbidities) that impact hyperuricemia, and made recommendations on pharmacologic ULT in a range of case scenarios of patients with disease activity manifested by acute and chronic forms of gouty arthritis, including chronic tophaceous gouty arthropathy (1). Each individual and specific statement is designated as a “recommendation,” in order to reflect the nonprescriptive nature of decision making for the hypothetical clinical scenarios.

So that the voting panel could focus on gout treatment decisions, a number of key assumptions were made, as described in part 1 of the guidelines (1). Importantly, each proposed recommendation assumed that correct diagnoses of gout and acute gouty arthritis attacks had been made for the voting scenario in question. For treatment purposes, it was also assumed that treating clinicians were competent, and considered underlying medical comorbidities (including diabetes mellitus, gastrointestinal disease, hypertension, and hepatic, cardiac, and renal disease) and potential drug toxicities and drug–drug interactions when making both treatment choices and dosing decisions on chosen pharmacologic interventions. The RAND/University of California at Los Angeles (UCLA) methodology used here emphasizes the level of evidence, safety, and quality of therapy, and excludes analyses of societal cost of health care. As such, the ACR gout guidelines are designed to reflect best practice, supported either by level of evidence or consensus-based decision making. These guidelines cannot substitute for individualized direct assessment of the patient, coupled with clinical decision making by a competent health care practitioner. The motivation, financial circumstances, and preferences of the gout patient also need to be considered in clinical practice, and it is incumbent on the treating clinician to weigh the issues not addressed by this methodology, such as treatment costs, when making management decisions. Last, the guidelines for gout management presented herein were not designed to determine eligibility for health care cost coverage by third party payors.

## Materials and methods

Utilizing the RAND/UCLA methodology (18), we conducted a systematic review, generated case scenarios, developed recommendations, and graded the evidence.

**Design: RAND/UCLA Appropriateness Method overview.** The RAND/UCLA method of group consensus was developed in the 1980s, incorporates both Delphi and nominal group methods (18), and has been successfully used to develop other guidelines commissioned by the ACR. The purpose of this methodology is to reach a consensus among experts, with an understanding that published literature may not be adequate to provide sufficient evidence for day-to-day clinical decision making. The RAND/UCLA method requires 2 groups of experts: a core expert panel (CEP) that provides input into case scenario development, and a task force panel (TFP) that votes on the case scenarios (1). A systematic review of pertinent literature was performed concurrently, and a scientific evidence report was generated. This evidence report was then given to the TFP, in conjunction with a variety of clinical scenarios and clinical decision-making questions of interest for each scenario.

The diverse TFP, totaling 11 people, consisted of rheumatologists in a community private practice (CK), a health maintenance organization practice (GL), and a Veterans Affairs practice (GK); a rheumatology physician–scientist inflammation researcher (BR); a rheumatologist with expertise in clinical pharmacology (DEF); a rheumatologist gout expert that is an Internal Medicine Residency Director (NLE); a rheumatologist gout expert that is a Chair of Internal Medicine (BM); 2 primary care internal medicine physicians (DJ, SAY); a nephrologist (VN); and a patient representative (SK) (1). There were 2 rounds of ratings, the first anonymous, with the members of the TFP instructed to rank each potential element of the guidelines on a risk/benefit Likert scale ranging from 1–9, followed by a face-to-face group discussion with revoting. A vote of 1–3 on the Likert scale was scored as *inappropriate*, where risks clearly outweigh the benefits; a vote of 4–6 was scored as *uncertain* (“lack of consensus”), where the risk/benefit ratio is uncertain; and a vote of 7–9 was scored as *appropriate*, where benefits clearly outweigh the risks. Case scenarios were translated into recommendations, where the median voting scores were 7–9 on the Likert scale (“appropriate”), and if there was no significant disagreement, defined as no more than one-third of the TFP voting below the Likert scale level of 7 in the question. The final rating was done anonymously in a 2-day face-to-face meeting led by an experienced internal medicine physician moderator (NW).

**Systematic review.** PubMed and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched to find all articles on gout with the help of an experienced librarian. PubMed is a database of medical literature from the 1950s to the present. CENTRAL includes references from PubMed, Embase, and the Cochrane Review Groups’ specialized registers of controlled trials and hand search results. We used search terminology (hedge) based on the Cochrane Highly Sensitive Search Strategy for identifying

randomized trials. The hedge was expanded to include articles discussing research design, cohort, case-control, and cross-sectional studies. Limits added to the hedge include English language and the exclusion of "animal only" studies. The searches for all 4 domains were conducted simultaneously and therefore included terms for hyperuricemia and other gout-related issues. Conducted on September 25, 2010, the search retrieved 5,830 articles from PubMed and CENTRAL. The review was divided into 3 stages: titles, abstracts from manuscripts, and entire manuscripts. At each stage, each title, abstract, or manuscript was included or excluded using prespecified rules, as described (1). Of the 5,830 titles, 192 duplicate titles and 82 non-English titles were excluded, with an additional 3,729 titles excluded based on exclusion criteria, leaving 1,827 titles, of which another 1,699 were excluded in the abstract phase. A total of 128 manuscripts remained that were further categorized into pharmacologic and non-pharmacologic studies (1). Subsequently, we updated our systematic review by repeating the search with the same criteria to include any articles that were published between September 25, 2010 and March 31, 2011, and we hand searched recent meeting abstracts from the ACR and EULAR for any randomized controlled trials that were yet to be published. The supplemental search resulted in 4 additional manuscripts and 5 meeting abstracts on pharmacologic agents, some of which were subsequently published and then reevaluated for evidence grade. Finally, there were 41 manuscripts on nonpharmacologic modalities (such as diet, alcohol, exercise, etc.) that included both retrospective and prospective studies, but all were excluded, since none were randomized controlled studies on interventions in gout patients. There were 87 manuscripts on pharmacologic agents for the treatment of patients with gout. Of these, 47 were randomized controlled trials and included in the evidence report, whereas the remaining 40 uncontrolled trials were excluded. A total of 21 manuscripts on ULT were separately addressed (1).

For this article (part 2 of the guidelines), a total of 30 manuscripts and 5 meeting abstracts were assessed, with 26 manuscripts and 2 meeting abstracts on acute gout and 4 manuscripts and 3 meeting abstracts on prophylaxis included in the evidence report and evaluated by the TFP.

**Case scenarios.** Through an interactive, iterative process, the CEP developed unique case scenarios of acute gouty attacks with varied treatment options, and the type of attack by severity, duration, and extent of the attack. The objective was to represent a broad spectrum of attacks that a clinician might see in a busy practice. For the case scenarios, the severity of acute gout differed based on self-reported worst pain on a 0–10 visual analog scale (VAS) (19,20). Pain  $\leq 4$  was considered mild, 5–6 was considered moderate, and  $\geq 7$  was considered severe (19,20). Case scenarios also varied by duration of the acute gout attack; we divided this into early ( $<12$  hours), well established (12–36 hours), and late ( $>36$  hours). Case scenarios also varied in the number of active joints involved: 1 or a few small joints, 1 or 2 large joints (ankle, knee, wrist, elbow, hip, or shoulder), and polyarticular involve-

ment (defined as either acute arthritis involving 3 separate large joints, or acute arthritis of 4 or more joints, with arthritis involving more than 1 "region" of joints). Joint regions were defined as: forefoot (metatarsal joints and toes), midfoot (tarsal joints), ankle/hindfoot, knee, hip, fingers, wrist, elbow, shoulder, or other (Figure 1). The management strategies presented were developed for case scenarios involving gouty arthritis, but the intent was that acute bursal inflammation due to gout (e.g., in the prepatellar or olecranon bursa) and small joint involvement would have comparable recommendations for overall management strategies.

**Developing recommendations from votes by the TFP and grading the evidence.** A priori recommendations were derived from only positive results (median Likert score  $\geq 7$ ). In the text below, all recommendations derived from TFP votes are denoted by an accompanying evidence grade. In addition to TFP vote results, the panel provided some statements based on discussion (not votes). Such statements are specifically described as discussion items (rather than TFP-voted recommendations) in the Results. We also comment on specific circumstances where the TFP did not vote a particularly important clinical decision-making item as appropriate (i.e., the median Likert score was  $\leq 6$  or there was a wide dispersion of votes despite a median score of  $\geq 7$ ). Samples of voting scenarios and results are shown in Supplemental Figure 1 (available in the online version of this article at [http://onlinelibrary.wiley.com/journal/10.1002/\(ISSN\)2151-4658](http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658)).

The level of evidence supporting each recommendation was ranked based on previous methods used by the American College of Cardiology (21) and applied to other recent ACR recommendations (22,23): level A grading was assigned to recommendations supported by more than 1 randomized clinical trial, or 1 or more meta-analyses; level B grading was assigned to the recommendations derived from a single randomized trial, or nonrandomized studies; and level C grading was assigned to consensus opinion of experts, case studies, or standard of care.

**Managing perceived potential conflict of interest (COI).** Potential COI was managed in a prospective and structured manner (1). All of the participants intellectually involved in the project, whether authors or not, were required to fully disclose their relationships with any of the companies with a material interest in gout, listed in Supplemental Appendix A (available in the online version of this article at [http://onlinelibrary.wiley.com/journal/10.1002/\(ISSN\)2151-4658](http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658)). Disclosures were identified at the start of the project and updated every 6 months. A summary listing of all perceived potential COI is available in Supplemental Appendix A (available in the online version of this article at [http://onlinelibrary.wiley.com/journal/10.1002/\(ISSN\)2151-4658](http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658)).

Based on the policies of the ACR, no more than 49% of the project participants were permitted to have COI at any given time, and a majority of the TFP was required to have no perceived potential COI. It was further required that the project principal investigator (JDF) remain without per-

Severity of Acute Gouty Arthritis Attack Intensity of attack based on self-reported pain (0-10 visual analog scale)	
Mild	≤ 4
Moderate	5-6
Severe	≥ 7

Duration of the gouty arthritis attack since onset	
Early	< 12 Hours after attack onset
Well-Established	12 to 36 Hours after attack onset
Late	> 36 Hours after attack onset

Extent of acute gouty arthritis attack Based on number of active joints	
One or a few small joints	
1 or 2 large* joints	
* defined as: ankle, knee, wrist, elbow, hip, shoulder	
Polyarticular	
• 4 or more joints, with arthritis involving more than 1 region <sup>§</sup>	
§ Regions defined as: forefoot (metatarsophalangeal joints, toes), midfoot (tarsal joints), ankle/hindfoot, knee, hip, fingers, wrist, elbow, shoulder, other	
• Acute gout attack involving 3 separate large joints is considered as a form of polyarticular gout for this scheme of management	

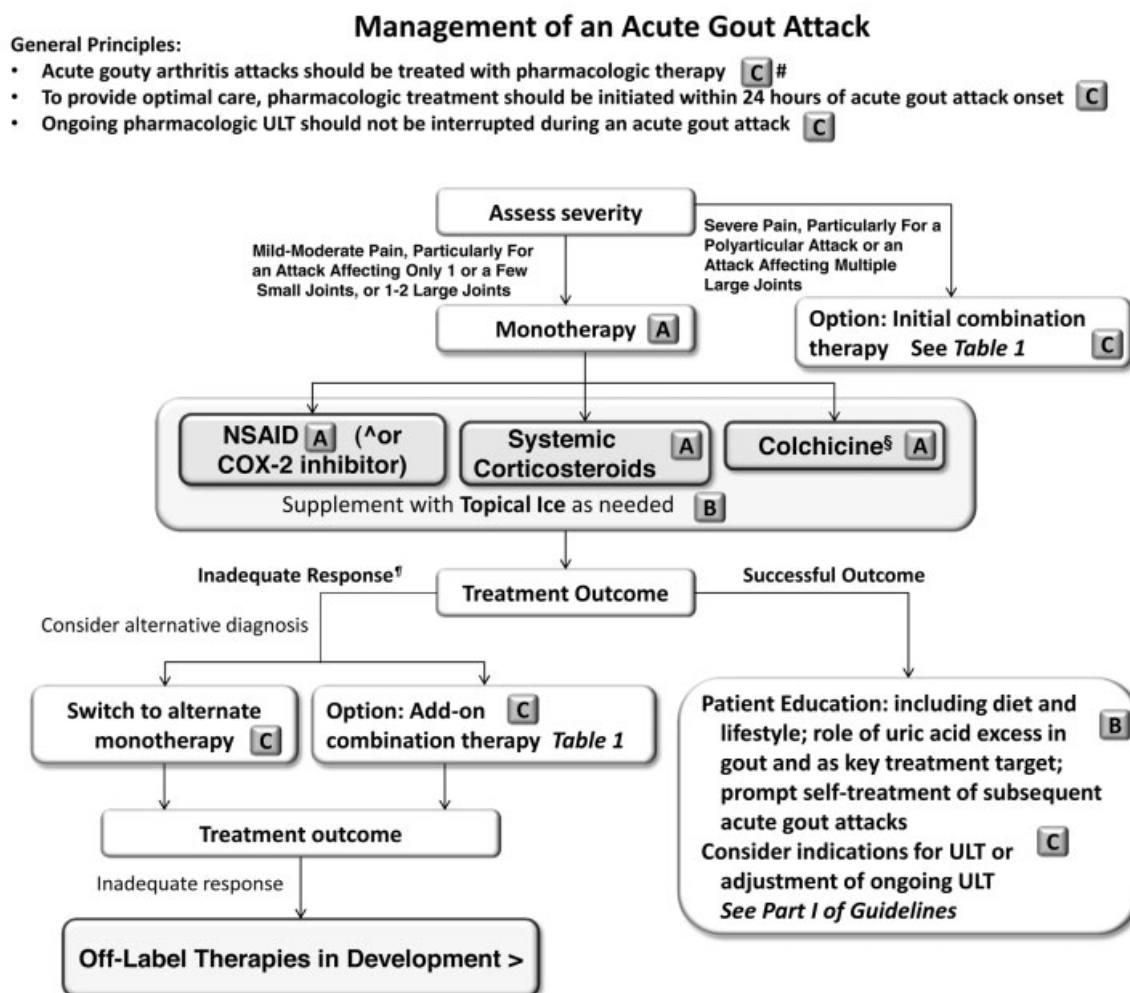
**Figure 1.** Case scenarios for defining acute gouty arthritis attack features. These case scenarios were generated by the core expert panel, and therapeutic decision-making options for these scenarios were voted on by the task force panel.

ceived potential COI during the guideline development process, and for an additional 12 months afterward.

## Results

**General principles for treatment of the acute attack of gouty arthritis (“acute gout” management).** Figure 2 summarizes the overall recommendations on treatment of an acute gouty arthritis attack. The TFP recommended that an acute gouty arthritis attack should be treated with pharmacologic therapy (evidence C), and that treatment should be preferentially initiated within 24 hours of onset of an acute gout attack (evidence C). The latter recommendation was based on consensus that early treatment leads to better patient-reported outcomes. The TFP also recommended continuing established pharmacologic ULT without interruption during an acute attack of gout (evidence C), i.e., do not stop ULT therapy during an acute attack. The TFP also recommended patient education, not simply on dietary and other triggers of acute gout attacks, but also providing the patients with instruction so that they can initiate treatment upon signs and symptoms of an acute gout attack, without the need to consult their health care practitioner for each attack (evidence B) (24). Moreover, fundamental patient education includes discussion that gout is caused by body excess of uric acid, and that only effective ULT is potentially “curative” (evidence B) (24).

**Initial pharmacologic treatment of the acute attack of gouty arthritis.** The TFP recommended that the choice of pharmacologic agent should be based upon severity of pain and the number of joints involved (Figure 2). For attacks of mild/moderate gout severity (≤6 of 10 on a 0–10 pain VAS) particularly those involving 1 or a few small joints or 1 or 2 large joints, the TFP recommended that initiating monotherapy was appropriate, with recommended options being oral nonsteroidal antiinflammatory drugs (NSAIDs), systemic corticosteroids, or oral colchicine (evidence A for all therapeutic categories) (25–28) (Figure 2). The TFP also voted that combination therapy was an appropriate option to consider when the acute gout attack was characterized by severe pain, particularly in an acute polyarticular gout attack or an attack involving 1–2 large joints (evidence C) (Figure 2). The TFP did not rank one therapeutic class over another. Therefore, it is at the discretion of the prescribing physicians to choose the most appropriate monotherapy based on the patient’s preference, prior response to pharmacologic therapy for an acute gout attack, and associated comorbidities. Recommendations for appropriate combination therapy options are highlighted in Table 1 and discussed below. The TFP did not vote on case scenarios for specific renal or hepatic function impairment–adjusted dosing and individual contraindications or drug–drug interactions with pharmacologic therapies (29–31).



# Evidence Grades for Recommendations:

**Level A:** Supported by multiple (ie, more than one) randomized clinical trials or meta-analyses

**Level B:** Derived from a single randomized trial, or nonrandomized studies.

**Level C:** Consensus opinion of experts, case studies, or standard-of-care.

§ Colchicine was recommended as an appropriate option for acute gout if started within 36 hours of symptom onset.

^ Selective COX-2 inhibition with agents available outside the USA such as etoricoxib (Evidence A) was recommended as an option in patients with GI contra-indications or intolerance to NSAIDs, but selective COX-2 inhibition shares many adverse events with NSAID therapy. COX-2 inhibition therapy with celecoxib (Evidence B) requires high doses and has unclear risk-benefit ratio at this time.

¶ Inadequate response is defined as

< 20% improvement in pain score within 24 hours or  
< 50% at ≥ 24 hours

> Off-label use of biologic IL-1 inhibitor treatment has been investigated for acute gout when non-biologic therapeutic categories are ineffective or contra-indicated, but this approach is not approved for gout by medical regulatory agencies at the time this is written.

**Figure 2.** Overview of management of an acute gout attack. This algorithm summarizes the recommendations by the task force panel on the overall approach to management of an acute attack of gouty arthritis, with further details, as expanded in other figures and tables, referenced in the figure and discussed in the text. ULT = urate-lowering therapy; NSAID = nonsteroidal antiinflammatory drug; COX-2 = cyclooxygenase 2; GI = gastrointestinal; IL-1 = interleukin-1.

**Table 1. Task force panel (TFP) recommendations for combination therapy approach to acute gouty arthritis**

Initial combination therapy is an appropriate option for an acute, severe gout attack, particularly with involvement of multiple large joints or polyarticular arthritis (evidence C)

Acceptable combination therapy approaches include the initial simultaneous use of full doses (or, where appropriate, prophylaxis doses) of either: 1) colchicine and nonsteroidal antiinflammatory drugs (NSAIDs), 2) oral corticosteroids and colchicine, or 3) intra-articular steroids with all other modalities (evidence C)

For patients not responding adequately to initial pharmacologic monotherapy, adding a second appropriate agent is an acceptable option (evidence C)\*

The TFP was not asked to vote on use of NSAIDs and systemic corticosteroids in combination, given core expert panel concerns about synergistic gastrointestinal tract toxicity

\* Assumes that the initial diagnosis of acute gout was correct, and that the lack of adequate response of acute gout was to an appropriate first-line therapy option.

**NSAIDs.** For NSAIDs, the TFP recommended full dosing at either the Food and Drug Administration (FDA)– or European Medical Agency–approved antiinflammatory/analgesic doses used for the treatment of acute pain and/or treatment of acute gout (evidence A–C) (27,28,32–34) (Figure 3A). The FDA has approved naproxen (evidence A) (34,35), indomethacin (evidence A) (27,28,32,33), and sulindac (evidence B) (36) for the treatment of acute gout. However, analgesic and antiinflammatory doses of other NSAIDs may be as effective (evidence B and C). For cyclooxygenase 2 (COX-2) inhibitors, as an option in patients with gastrointestinal contraindications or intolerance to NSAIDs, published randomized controlled trials support the efficacy of etoricoxib (evidence A) and lumiracoxib (evidence B) (25,37,38), but these agents are not available in the US, and lumiracoxib has been withdrawn from use in several countries due to hepatotoxicity. A randomized controlled trial of a single comparison of celecoxib versus indomethacin (39) suggested effectiveness of a high-dose celecoxib regimen (800 mg once, followed by 400 mg on day 1, then 400 mg twice daily for a week) in acute gout. The TFP recommended this celecoxib regimen as an option for acute gout in carefully selected patients with contraindications or intolerance to NSAIDs (evidence B), keeping in mind that the risk/benefit ratio is not yet clear for celecoxib in acute gout.

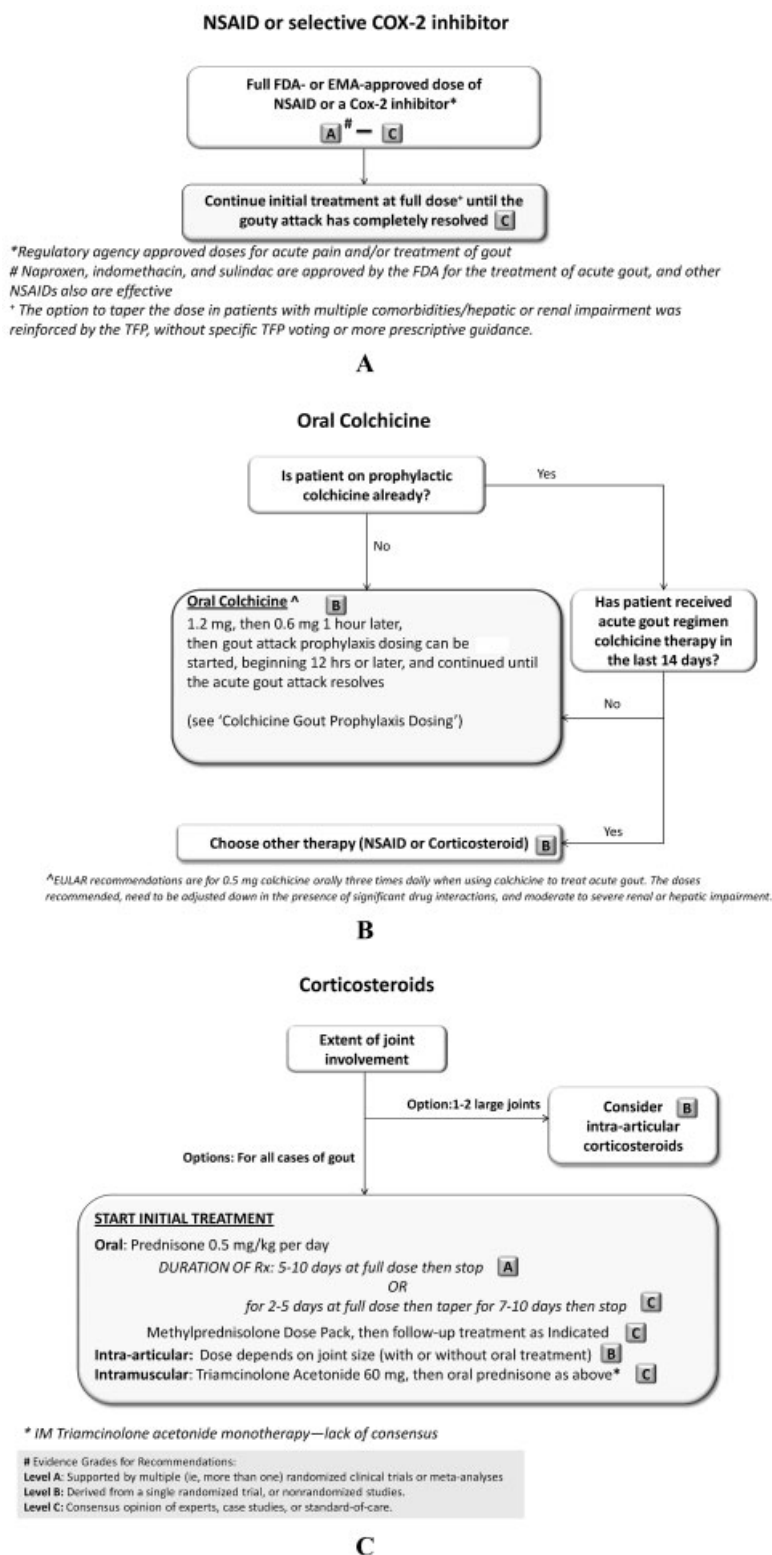
The TFP did not reach a consensus to preferentially recommend any one specific NSAID as first-line treatment. The TFP did recommend continuing the initial NSAID inhibitor treatment regimen at the full dose (if appropriate) until the acute gouty attack completely resolved (evidence C). The option to taper the dose in patients with multiple comorbidities/hepatic or renal impairment was reinforced by the TFP, without specific TFP voting or more prescriptive guidance. Last, there was no TFP consensus on the use of intramuscular ketorolac or topical NSAIDs for the treatment of acute gout.

**Colchicine.** The TFP recommended oral colchicine as one of the appropriate primary modality options to treat acute gout, but only for gout attacks where the onset was no greater than 36 hours prior to treatment initiation (evidence C) (Figure 3B). The TFP recommended that acute gout can be treated with a loading dose of 1.2 mg of colchicine followed by 0.6 mg 1 hour later (evidence B) (10), and this regimen can then be followed by gout attack prophylaxis dosing 0.6 mg once or twice daily (unless dose adjustment is required) 12 hours later, until the gout attack resolves (evidence C) (26). For countries where 1.0 mg or 0.5 mg rather than 0.6 mg tablets of colchicine are available, the TFP recommended, as appropriate, 1.0 mg colchicine as the loading dose, followed by 0.5 mg 1 hour later, and then followed, as needed, after 12 hours, by continued colchicine (up to 0.5 mg 3 times daily) until the acute attack resolves (evidence C). In doing so, the TFP rationale was informed by pharmacokinetics of the low-dose colchicine regimen, where the exposure to the drug in plasma becomes markedly reduced ~12 hours after administration in healthy volunteers (26). The TFP also evaluated prior EULAR recommendations on a colchicine dosing regimen for acute gout (0.5 mg 3 times daily) and the BSR-recommended maximum dosage for acute gout of 2 mg colchicine per day (10,12).

The algorithm in Figure 3B outlines recommendations for colchicine based on FDA labeling and TFP deliberations and votes, including specific recommendations for patients already receiving colchicine acute gout attack prophylaxis. For more specific prescriptive guidance, practitioners should consult the FDA-approved drug labeling, including recommended dosing reduction in moderate to severe chronic kidney disease (CKD) (40,41), and colchicine dose reduction (or avoidance of colchicine use) with drug interactions with moderate to high potency inhibitors of cytochrome P450 3A4 and of P-glycoprotein; major colchicine drug interactions include those with clarithromycin, erythromycin, cyclosporine, and disulfiram (30,31). Last, the TFP did not vote on use of intravenous colchicine, since the formulation is no longer available in the US, due to misuse and associated severe toxicity.

**Systemic and intraarticular corticosteroids and adrenocorticotrophic hormone (ACTH).** When selecting corticosteroids as the initial therapy, the TFP recommended to first consider the number of joints with active arthritis. For involvement of 1 or 2 joints, the TFP recommended the use of oral corticosteroids (evidence B); the TFP additionally recommended the option of intraarticular corticosteroids for acute gout of 1 or 2 large joints (evidence B) (42) (Figure 3C). For intraarticular corticosteroid therapy in acute gouty arthritis, it was recommended that dosing be based on the size of the involved joint(s), and that this modality could be used in combination (Table 1) with oral corticosteroids, NSAIDs, or colchicine (evidence B) (42). Specific doses for intraarticular corticosteroid therapy in specific joints were not considered during TFP voting.

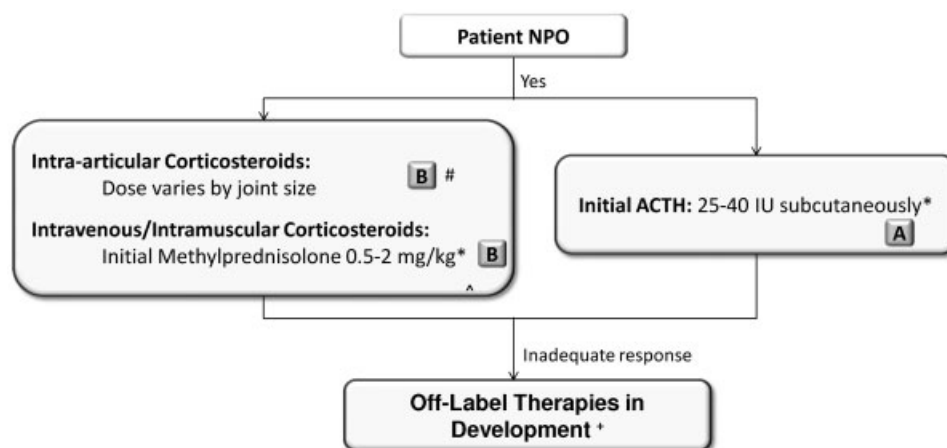
Where intraarticular joint injection is impractical (e.g., polyarticular joint involvement, patient preference, or injection of the involved joint site is not in the scope of the provider's usual practice), the TFP recommended oral cor-



**Figure 3.** Recommendations for the individual pharmacologic monotherapy options for an acute gouty arthritis attack. The figure is separated into distinct parts that schematize use of the first-line therapy options (A, nonsteroidal antiinflammatory drugs [NSAIDs], B, colchicine, and C, corticosteroids), and specific recommendations by the task force panel (TFP). COX-2 = cyclooxygenase 2; FDA = Food and Drug Administration; EMA = European Medical Agency; EULAR = European League Against Rheumatism; IM = intramuscular.

ticosteroids, prednisone, or prednisolone at a starting dosage of at least 0.5 mg/kg per day for 5–10 days, followed by discontinuation (evidence A) (28,43), or alternately, 2–5

days at the full dose, followed by tapering for 7–10 days, and then discontinuation (evidence C). Acknowledging current prevalence of usage, the TFP recommended, as an



\* Can be repeated. Subsequent dose will be determined based on initial response.

^Lack of consensus: IM Triamcinolone acetonide monotherapy, and IM Ketorolac NSAID therapy.

\* Off-label biologic IL-1 inhibitor treatment, such as with anakinra, has not been approved by medical regulatory agencies for gout at the time this is written, and has unclear risk-benefit ratio.

# Evidence Grades for Recommendations:

**Level A:** Supported by multiple (ie, more than one) randomized clinical trials or meta-analyses

**Level B:** Derived from a single randomized trial, or nonrandomized studies.

**Level C:** Consensus opinion of experts, case studies, or standard-of-care.

**Figure 4.** Acute gouty arthritis attack management in the nothing by mouth (NPO) patient. The figure schematizes options for management of acute gout in the patient unable to take oral antiinflammatory medications, and specific recommendations by the task force panel on decision making in this setting. ACTH = adrenocorticotrophic hormone; IL-1 = interleukin-1; IM = intramuscular; NSAID = nonsteroidal antiinflammatory drug.

appropriate option according to provider and patient preference, the use of an oral methylprednisolone dose pack for initial treatment of an acute attack of gout (evidence C).

The TFP also recommended, as appropriate in each case scenario, an alternative regimen of intramuscular single-dose (60 mg) triamcinolone acetonide, followed by oral prednisone or prednisolone (evidence C). However, there was no consensus by the TFP on the use of intramuscular triamcinolone acetonide as monotherapy. Last, the TFP vote also did not reach a consensus on use of ACTH (evidence A) for acute gout in patients able to take medications orally, but did consider ACTH in separate voting, as described below, for patients unable to take oral antiinflammatory medications.

**Initial combination therapy for acute gout.** For patients with severe acute gout attack ( $\geq 7$  of 10 on a 0–10 pain VAS) and patients with an acute polyarthritis or involvement of more than 1 large joint, the TFP recommended, as an appropriate option, the initial simultaneous use of full doses (or, where appropriate, a full dose of 1 agent and prophylaxis dosing of the other) of 2 of the pharmacologic modalities recommended above. Specifically, the TFP recommended the option to use combinations of colchicine and NSAIDs, oral corticosteroids and colchicine, or intra-articular steroids with any of the other modalities (evidence C). The TFP was not asked by the CEP to vote on use of NSAIDs and systemic corticosteroids in combination,

given CEP concerns about synergistic gastrointestinal tract toxicity of that drug combination.

**Inadequate response of an acute gout attack to initial therapy.** There is a lack of a uniform definition of an inadequate response to the initial pharmacologic therapy for an acute attack of gouty arthritis (2,26,44). Clinical trials in acute gout have defined variable primary end points for therapeutic response, such as percent improvement in pain on a Likert scale or VAS. To define inadequate response for scenarios in this section, the CEP asked the TFP to vote on various percent improvement definitions at time points such as 24, 48, or 72 hours. The TFP voted that the following criteria would define an inadequate response of acute gout to pharmacologic therapy in case scenarios: either  $<20\%$  improvement in pain score within 24 hours or  $<50\%$  improvement in pain score  $\geq 24$  hours after initiating pharmacologic therapy.

For the scenario of a patient with an acute attack of gouty arthritis not responding adequately to initial pharmacologic monotherapy, the TFP advised, without a specific vote, that alternative diagnoses to gout should be considered (Figure 2 and Table 1). For patients not responding to initial therapy, the TFP also recommended switching to another monotherapy recommended above (evidence C) or adding a second recommended agent (evidence C). Use of a biologic interleukin-1 (IL-1) inhibitor (anakinra 100 mg subcutaneously daily for 3 consecutive

days; evidence B) (44,45) or canakinumab 150 mg subcutaneously (46,47) as an option for severe attacks of acute gouty arthritis refractory to other agents was graded as evidence A in the systematic review. Given a lack of randomized studies for anakinra (44,45) and the unclear risk/benefit ratio and lack of FDA approval for canakinumab (46,47) at the time this was written, the authors, independent of TFP discussion, assessed the role of IL-1 inhibitor therapy in acute gout as uncertain.

#### **Case scenarios for the nothing by mouth (NPO) patient.**

Acute gout attacks are common in the in-hospital setting, where patients may be NPO due to different surgical and medical conditions. In such a scenario, the TFP recommended intraarticular injection of corticosteroids for involvement of 1 or 2 joints (with the dose depending on the size of the joint; evidence B) (42) (Figure 4). The TFP also recommended, as appropriate options, intravenous or intramuscular methylprednisolone at an initial dose at 0.5–2.0 mg/kg (evidence B) (48).

The TFP also recommended, as an appropriate alternative for the NPO patient, subcutaneous synthetic ACTH at an initial dose of 25–40 IU (evidence A) (49), with repeat doses as clinically indicated (for either ACTH or intravenous steroid regimens). There was no voting by the TFP on specific followup ACTH or an intravenous steroid dosing regimen, given a lack of evidence. In the scenario of the NPO patient with acute gout, there was no consensus on the use of intramuscular ketorolac or intramuscular triamcinolone acetone monotherapy. Biologic IL-1 inhibition therapy remains an FDA-unapproved modality for NPO patients, without specific past evaluation in this population.

#### **Critical drug therapy adverse event considerations in acute gout.**

It was not possible to evaluate every permutation of gout treatment and comorbid disease, given the constraints of the project. The treating clinician will need to carefully weigh the complexities of each unique patient. TFP discussions emphasized that potential drug toxicities due to comorbidities and drug–drug interactions are considerable in treatment of acute gout (30,31). Some examples include underlying moderate and severe CKD (NSAIDs, COX-2 inhibitors, colchicine), congestive heart failure (NSAIDs, COX-2 inhibitors), peptic ulcer disease (NSAIDs, COX-2 inhibitors, corticosteroids), anticoagulation or antiplatelet aggregation therapy (NSAIDs), diabetes mellitus (corticosteroids), ongoing infection or high risk of infection (corticosteroids), and hepatic disease (NSAIDs, COX-2 inhibitors, colchicine) (30,31).

**Complementary therapies for acute gout attack.** The TFP recommended topical ice application to be an appropriate adjunctive measure to 1 or more pharmacologic therapies for acute gouty arthritis (evidence B) (50). The TFP voted, as inappropriate, the use of a variety of oral complementary agents for the treatment of an acute attack (cherry juice or extract, salicylate-rich willow bark extract, ginger, flaxseed, charcoal, strawberries, black currant, burdock, sour cream, olive oil, horsetail, pears, or celery root).

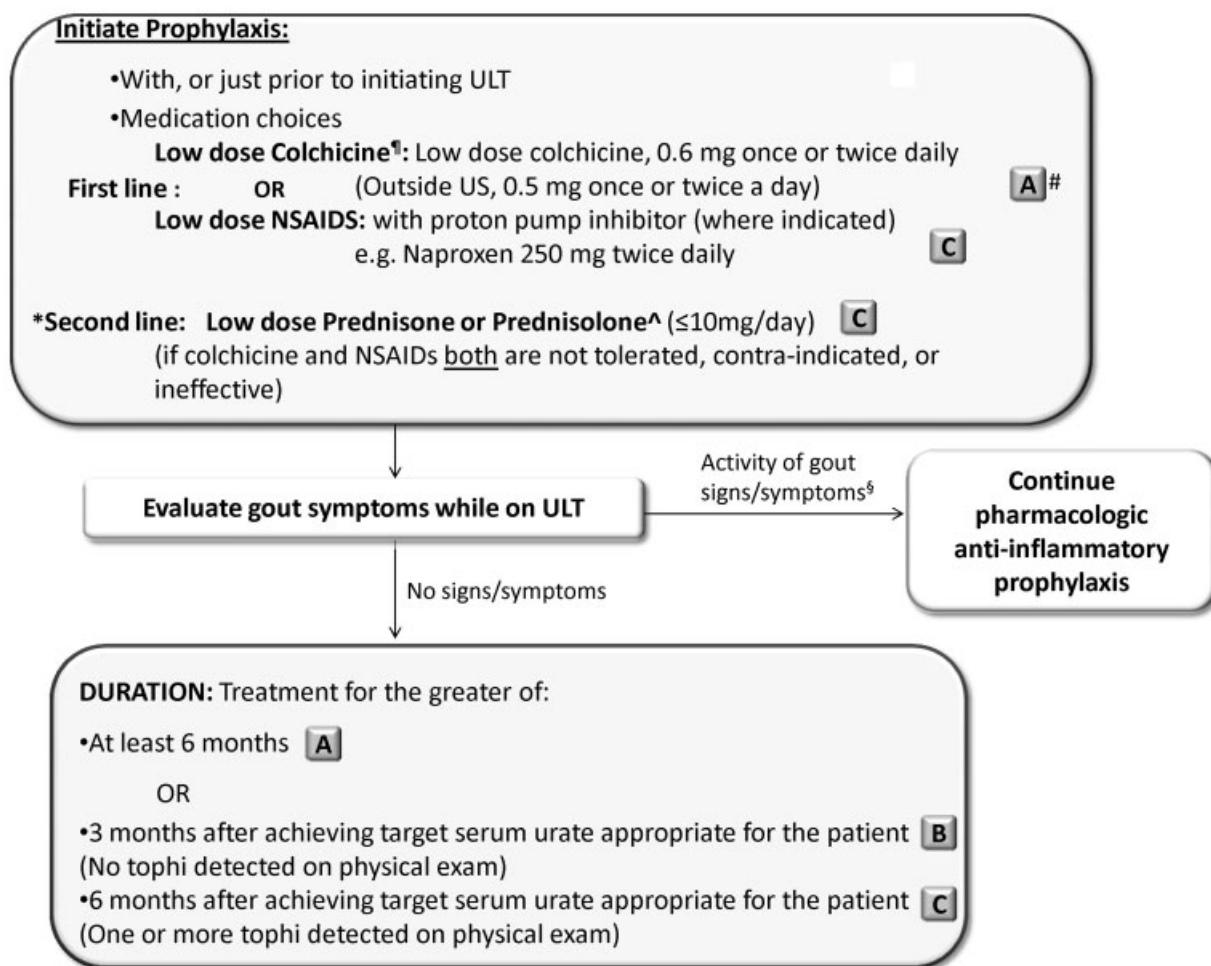
#### **Recommendations for pharmacologic antiinflammatory prophylaxis of attacks of acute gout**

The TFP recommended pharmacologic antiinflammatory prophylaxis for all case scenarios of gout where ULT was initiated, given high gout attack rate frequencies in early ULT (evidence A) (51–54) (Figure 5). For gout attack prophylaxis, the TFP recommended, as a first-line option, use of oral colchicine (evidence A) (54,55). The TFP also recommended, as a first-line option (with a lower evidence grade than for colchicine), the use of low-dose NSAIDs (such as naproxen 250 mg orally twice a day), with proton-pump inhibitor therapy or other effective suppression therapy for peptic ulcer disease and its complications, where indicated (evidence C) (54).

In their evaluation of colchicine evidence in gout attack prophylaxis, the TFP specifically recommended low-dose colchicine (0.5 mg or 0.6 mg orally once or twice a day, with dosing further adjusted downward for moderate to severe renal function impairment and potential drug–drug interactions) (30) as appropriate for gout attack prophylaxis. The TFP did not vote on specific quantitative renal function impairment–adjusted dosing of oral colchicine. Since a pharmacokinetic analysis suggesting colchicine dose should be decreased by 50% below a creatinine clearance of 50 ml/minute is unpublished in peer-review form (41), specific quantitative colchicine dose adjustment in CKD is the decision of the treating clinician.

The TFP, in discussion without a specific vote, recognized the evidence that colchicine and low-dose NSAID prophylaxis fail to prevent all gout attacks in patient populations after initiation of ULT (51–54). As an alternative gout attack prophylaxis strategy in patients with intolerance or contraindication or refractoriness to both colchicine and NSAIDs, the TFP recommended use of low-dosage prednisone or prednisolone (defined here as  $\leq 10$  mg/day) (evidence C). Nevertheless, concerns were raised in discussion among the TFP and by the other authors regarding particularly sparse evidence for efficacy of this low-dose strategy. Given the known risks of prolonged use of corticosteroids, the authors urge clinicians to be particularly attentive in reevaluating the risk/benefit ratio of continued corticosteroid prophylaxis as the risk of acute gout attack decreases with time in conjunction with effective ULT. The TFP voted the use of high daily doses (i.e.,  $>10$  mg daily) of prednisone or prednisolone for gout attack prophylaxis to be as inappropriate in most case scenarios, and there was a lack of TFP consensus for more severe forms of chronic tophaceous gouty arthropathy. Last, there was a lack of TFP consensus on the risk/benefit ratio for off-label use of biologic IL-1 inhibition (evidence A) (56,57) for antiinflammatory gout attack prophylaxis in patients who previously failed or had intolerance or contraindications to low doses of colchicine, NSAIDs, and prednisone or prednisolone for gout attack prophylaxis.

**Duration of antiinflammatory prophylaxis of acute gout attacks.** The TFP recommended to continue pharmacologic gout attack prophylaxis if there is any clinical evidence of continuing gout disease activity (such as 1 or



<sup>^</sup>Without specific task force panel (TFP) vote, the TFP advised that this measure requires particular, continued attention to risk-benefit ratio

<sup>§</sup> Examples include: acute gouty arthritis in the past 3 months, presence of palpable tophus or tophi, chronic tophaceous gouty arthropathy (with chronic synovitis) in the past 3 months

<sup>\*</sup>Lack of consensus: Prednisone/prednisolone at doses above 10 mg/day.

<sup>¶</sup> The TFP did not specifically address case scenarios involving renal impairment adjusted colchicine dosing for gout attack prophylaxis

#### # Evidence Grades for Recommendations:

**Level A:** Supported by multiple (ie, more than one) randomized clinical trials or meta-analyses

**Level B:** Derived from a single randomized trial, or nonrandomized studies.

**Level C:** Consensus opinion of experts, case studies, or standard-of-care.

**Figure 5.** Pharmacologic antiinflammatory prophylaxis of gout attacks and its relationship to pharmacologic urate-lowering therapy (ULT). The figure provides an algorithm for use of antiinflammatory prophylaxis agents to prevent acute gout attacks. The schematic highlights specific recommendations by the TFP on decision making on the initiation, options, and duration of prophylaxis relative to pharmacologic ULT therapy, relative to achievement of the treatment objectives of ULT. NSAIDs = nonsteroidal antiinflammatory drugs.

more tophi detected on physical examination, recent acute gout attacks, or chronic gouty arthritis), and/or the serum urate target has not yet been achieved (1). Specifically, the TFP voted to continue the prophylaxis for the greater of:

1) 6 months' duration (evidence A) (51,53,54), 2) 3 months after achieving the target serum urate level for the patient without tophi detected on physical examination (evidence B), or 3) 6 months after achieving the target serum urate

level, where there has been resolution of tophi previously detected on physical examination (evidence C) (Figure 5).

## Discussion

Acute attacks of gout have a detrimental impact on the quality of life of the patient due to pain and dysfunction of affected joints, and acute gout can have a substantial economic and societal impact (58–60). Following a systematic review of the literature and use of a formal group assessment process, we provide the first ACR guidelines for the therapy and antiinflammatory prophylaxis of acute gout attacks.

The TFP recommended multiple modalities (NSAIDs, corticosteroids by different routes, and oral colchicine) as appropriate initial therapeutic options for acute gout attacks. The TFP was informed in part by recent direct comparison studies suggesting approximate equivalency of oral systemic corticosteroids with NSAIDs (28,43). Essentially, the TFP concluded, without a specific vote, that selection of treatment choice is that of the prescribing clinician, and to be based upon factors including patient preference, the patient's previous response to pharmacologic therapies, associated comorbidities and, in the unique case of colchicine, the time since onset of the acute gout attack. The dosing adjustments and relative and absolute contraindications for NSAIDs and colchicine due to associated comorbidities (such as renal and hepatic impairment) and drug interactions were not addressed in these guidelines. There is published literature addressing these issues (30,31) such as quality indicators for safe use of NSAIDs (61–63), including ACR quality indicators for treatment of gout (64).

The TFP recommended a novel set of strict limitations on colchicine doses for acute gout, starting with no more than 1.8 mg over 1 hour in the first 12-hour period of treatment (evidence B) (26), a paradigm shift from widespread prior use of this drug in clinical practice (10,12), but in accordance with FDA guidance. Prior EULAR and BSR recommendations on colchicine dosing for acute gout (10,12) and colchicine low-dose regimen pharmacokinetics (26) informed the TFP recommendation of low-dose colchicine (at a maximum of 0.6 mg twice daily) as a continuation option for an acute gout attack, if started at least 12 hours following the initial low-dose regimen.

For patients with polyarticular joint involvement and severe presentations of gout in 1 or 2 large joints, the TFP recommended, as appropriate, certain first-line combination therapy approaches. Although there is a lack of published randomized controlled trial data to support these recommendations, a large survey of rheumatologists in the US has shown that combination therapy for acute gout is often employed (65).

With respect to antiinflammatory prophylaxis of acute gout attacks, low-dose colchicine or low-dose NSAIDs were recommended as acceptable first-line options by the TFP, with a higher evidence level for colchicine. The use of low-dose colchicine or an NSAID in gout attack prophylaxis is also recommended by EULAR (10). To date, in small clinical trials, low-dose daily oral colchicine was effective in preventing acute gout attacks (3,55), with supportive post hoc analyses in ULT trials (54). The efficacy of

low-dose NSAIDs for gout attack prophylaxis also was described in the febuxostat clinical trial program (54); however, prophylaxis was not the primary focus of the trials. Importantly, recent clinical trials of ULT agents have shown substantial rates of acute gout attacks in the first 6 months after the initiation of ULT, even when prophylaxis with colchicine 0.6 mg daily or low-dose NSAID therapy is administered (51–54). It is noteworthy that the TFP recommended prednisone or prednisolone  $\leq 10$  mg daily as a second-line option for acute gout prophylaxis, with the caveat that there is a lack of published robust data for the use of low-dose oral prednisone for gout prophylaxis. More investigation is needed to improve management for this clinical problem. Assessment of modulation of cardiovascular event risks by colchicine prophylaxis or by NSAIDs (66) in patients with gout would be particularly informative.

Limitations of the recommendations presented in this article include that only  $\sim 30\%$  were based on level A evidence, with approximately half based on level C evidence; this indicates the need for more studies in the aspects of gout management considered here. The process used here was limited by the current trial designs for assessment of acute gout therapies and prophylaxis of antiinflammatory pharmacologic agents in gout. For acute gout studies, most studies were on NSAIDs and involved an active comparator and noninferiority trial design. However, the majority of these studies failed to provide a noninferiority margin, which needs to be defined a priori to assess the validity of these trials. Although the majority of studies assessed pain as the primary outcome for the acute gout trials, there is a lack of a single uniform measure that precludes meta-analysis. Furthermore, there is a lack of consensus on what time period after initiation of therapy constitutes a primary response, since trials ranged from a few hours to 10 days. With the exception of recent analyses of biologic IL-1 inhibitors (56,57), there was a lack of robust clinical trials of gout attack prophylaxis using antiinflammatory pharmacologic agents. Also, the primary measure in these trials is the recurrence of self-reported acute gout attacks, an outcome that has not been validated using Outcome Measures in Rheumatology criteria (67). Efforts are underway to precisely define acute gout attack in gout clinical trials (68). Last, the RAND/UCLA methodology did not address important societal and patient preference issues on treatment costs and cost-effectiveness comparisons between medication choices for acute gout and pharmacologic prophylaxis of acute gout attacks. This is already a pressing question with respect to use of agents, including colchicine and COX-2 selective inhibitors, and would be expected to emerge as a larger issue if biologic IL-1 inhibitors, in late-stage clinical development after phase III studies at the time this was written, obtain regulatory approval for acute gout treatment and prophylaxis.

In summary, these guidelines, the first from the ACR for the management and antiinflammatory prophylaxis of acute attacks of gouty arthritis, have been developed to provide recommendations to clinicians treating patients with gout. The ACR plans to update these guidelines to capture future treatments or advances in the

management and prophylaxis of acute gout, and as the risk/benefit ratios of emerging therapies are further investigated.

**Addendum.** Therapies that were approved after the original literature review, or diet and lifestyle measures studied after the original literature review, are not included in these recommendations.

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## AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Terkeltaub had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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# EXHIBIT C

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(12) **United States Patent**  
**Davis**

(10) **Patent No.:** **US 7,964,647 B2**  
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(54) **COLCHICINE COMPOSITIONS AND METHODS**

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(60) Provisional application No. 60/977,796, filed on Oct. 5, 2007, provisional application No. 61/090,965, filed on Aug. 22, 2008.

(51) **Int. Cl.**

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(52) **U.S. Cl.** ..... **514/629**; 564/123; 564/308; 564/427; 568/306

(58) **Field of Classification Search** ..... None  
See application file for complete search history.

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**ABSTRACT**

Stable ultrapure colchicine compositions comprising ultrapure colchicine and a pharmaceutically acceptable excipient are described. The compositions can be tablets. Methods for preparing such compositions and methods of use are also disclosed. Methods of treating gout flares with colchicine compositions are also disclosed.

**1 Claim, 1 Drawing Sheet**

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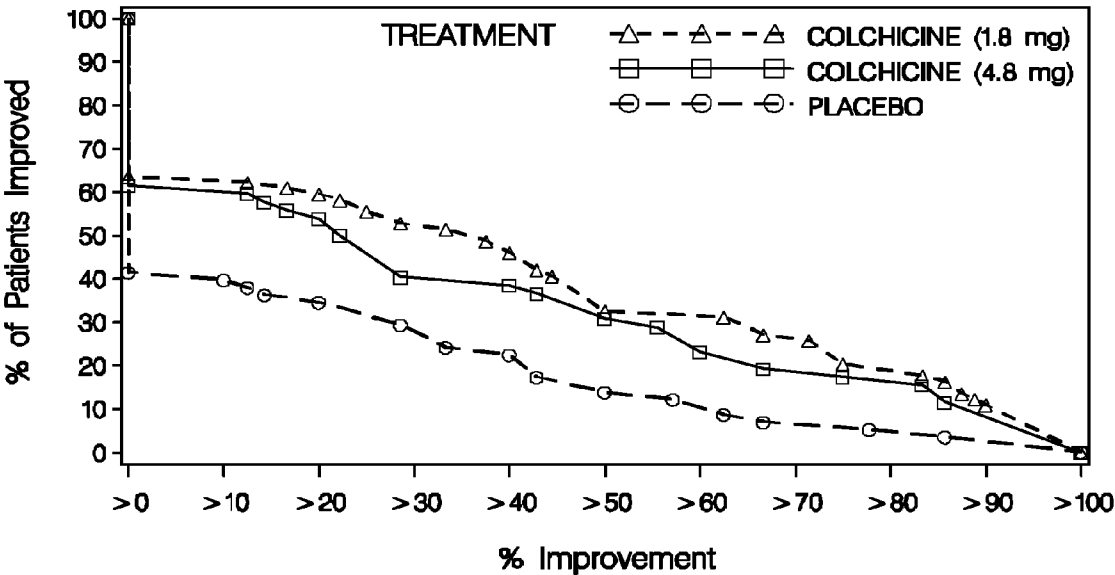
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U.S. Patent

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FIGURE 1



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COLCHICINE COMPOSITIONS AND  
METHODSCROSS REFERENCE TO RELATED  
APPLICATION

This application is a continuation of U.S. application Ser. No. 12/246,034, filed Oct. 6, 2008, which claims the benefit of U.S. Provisional Application Ser. No. 60/977,796 filed Oct. 5, 2007 and U.S. Provisional Application Ser. No. 61/090,965 filed Aug. 22, 2008, each of which is hereby incorporated by reference in its entirety.

## BACKGROUND

This application relates to colchicine compositions for therapeutic purposes, specifically ultrapure colchicine, and methods of making and using the colchicine compositions.

Colchicine, chemical name (-)-N-[(7S,12aS)-1,2,3,10-tetramethoxy-9-oxo-5,6,7,9-tetrahydrobenzo[a]heptalen-7-yl]-acetamide, is a pale yellow powder soluble in water in 1:25 dilution.

Colchicine is an alkaloid found in extracts of certain plants such as *Colchicum autumnale* and *Gloriosa superba*. Colchicine arrests cell division in animals and plants. It has adversely affected spermatogenesis in humans and in some animal species under certain conditions.

Gout (or gouty arthritis) is a disease caused by a build up of uric acid due to an overproduction of uric acid or a reduced ability of the kidney to get rid of uric acid. It is more common in males, postmenopausal women, and people with high blood pressure. Heavy alcohol use, diabetes, obesity, sickle cell anemia, and kidney disease also increase the risk. The condition may also develop in people who take drugs that interfere with uric acid excretion.

In gout, monosodium urate or uric acid crystals are deposited on the articular cartilage of joints, tendons and surrounding tissues due to elevated concentrations of uric acid in the blood stream. This provokes an inflammatory reaction of these tissues. Gout is characterized by excruciating, sudden, unexpected, burning pain, as well as swelling, redness, warmth, and stiffness in the affected joint. Low-grade fever may also be present. The patient usually suffers from two sources of pain. The crystals inside the joint cause intense pain whenever the affected area is moved. The inflammation of the tissues around the joint also causes the skin to be swollen, tender and sore if it is even slightly touched. For example, a blanket or even the lightest sheet draping over the affected area could cause extreme pain.

Acute gouty arthritis (alternatively referred to as a gout flare or a gout attack) is a sudden attack of pain in affected joints, especially in the feet and legs. Chronic gout involves repeated attacks of joint pain.

In acute gouty arthritis, symptoms develop suddenly and usually involve only one or a few joints. The big toe, knee, or ankle joints are most often affected. The pain frequently starts during the night and is often described as throbbing, crushing, or excruciating. The joint appears infected with signs of warmth, redness, and tenderness. The attacks of painful joints may go away in several days, but may return from time to time. Subsequent attacks usually last longer. Some people may progress to chronic gout (chronic gouty arthritis), while others may have no further attacks.

If several attacks of gout occur each year, it can lead to joint deformity and limited motion in joints. Uric acid deposits, called tophi, develop in cartilage tissue, tendons, and soft tissues. These tophi usually develop only after a patient has

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suffered from the disease for many years. Deposits also can occur in the kidneys, leading to chronic kidney failure.

Colchicine can be used for treating adults with acute gouty arthritis and pain in attacks of acute gouty arthritis, and also can be used beneficially for treating adults with chronic gout for prophylaxis of acute gout flares. Although its exact mode of action in the relief of gout is not completely understood, colchicine is known to decrease the inflammatory response to urate crystal deposition by inhibiting migration of leukocytes, to interfere with urate deposition by decreasing lactic acid production by leukocytes, to interfere with kinin formation and to diminish phagocytosis and the subsequent anti-inflammatory response. The anti-inflammatory effect of colchicine is relatively selective for acute gouty arthritis. However, other types of arthritis occasionally respond. It is neither an analgesic nor a uricosuric and will not prevent progression to chronic gouty arthritis. It does have a prophylactic, suppressive effect that helps to reduce the incidence of acute attacks and to relieve the residual pain and mild discomfort that patients with gout occasionally experience. In some instances, non-steroidal anti-inflammatory drugs (NSAIDs) may also be prescribed to relieve pain and inflammation in acute gouty arthritis attacks. Strong painkillers, such as codeine, or corticosteroids may also be prescribed to relieve the pain.

Colchicine is rapidly absorbed from the gastrointestinal tract. Peak concentrations occur in 0.5 to 2 hours. The drug and its metabolites are distributed in leukocytes, kidneys, liver, spleen and the intestinal tract. Colchicine is metabolized in the liver and excreted primarily in the feces with 10 to 20% eliminated unchanged in the urine.

There remains a need for pure forms of colchicine having low levels of impurities for pharmaceutical use to minimize the potential for side effects in patients taking colchicine pharmaceutical products and to minimize the need for costly toxicity testing required for approval of pharmaceutical products comprising conventional colchicine having high levels of individual or total impurities. In particular, there is a need for stable compositions comprising ultrapure colchicine.

## SUMMARY

Disclosed herein are colchicine compositions.

In one embodiment, the colchicine composition comprises ultrapure colchicine, wherein the ultrapure colchicine comprises no more than about 3.0% total impurities, specifically no more than about 2.0% total impurities, and a pharmaceutically acceptable excipient.

In another embodiment, the colchicine composition comprises ultrapure colchicine, wherein the ultrapure colchicine comprises no more than 3.0% total impurities, specifically no more than about 2.0% total impurities, a filler, a binder, and a disintegrant.

In yet another embodiment, the colchicine composition comprises about 0.6 mg A colchicine, about 12 to about 16 mg pregelatinized starch, about 20 to about 24 mg microcrystalline cellulose, about 3.9 to about 4.7 mg sodium starch glycolate, about 0.5 to about 0.7 mg magnesium stearate, and an amount of lactose monohydrate such that the colchicine dosage form has a total weight of about 100 mg.

In an embodiment, the colchicine composition comprises colchicine; and a pharmaceutically acceptable excipient; wherein the colchicine composition comprises no more than about 3.5% total impurities and no more than 0.42% N-deacetyl-N-formyl colchicine.

In an embodiment, the colchicine composition comprises colchicine; and a pharmaceutically acceptable excipient,

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wherein the colchicine composition has 0.6 mgA colchicine, wherein a single dose of the 0.6 mgA colchicine composition has enhanced bioavailability as compared to a single dose of a pharmaceutical product comprising 0.5 mg colchicine after potency correction for colchicine.

In an embodiment, the colchicine composition comprises colchicine; and a pharmaceutically acceptable excipient, wherein the colchicine composition has equivalent bioavailability when administered in a fed or a fasted state.

In an embodiment, the colchicine composition comprises colchicine; and a pharmaceutically acceptable excipient, wherein administration of a single dose of the colchicine composition to a human provides a Cmax between about 1.3 ng/mL and about 4.0 ng/mL, an AUC<sub>0- $\infty$</sub>  between about 4.4 ng-hr/mL and about 30.8 ng-hr/mL, or an AUC<sub>0- $\infty$</sub>  between about 6.7 ng-hr/mL and about 27.8 ng-hr/mL.

Methods of making the colchicine compositions are also disclosed herein.

In an embodiment, the method comprises wet granulating ultrapure colchicine, wherein the ultrapure colchicine comprises no more than about 3.0% of total impurities, with a pharmaceutically acceptable excipient to obtain wet granules, and mixing the granules with a disintegrant to obtain the composition.

In yet another embodiment, the method comprises wet granulating colchicine with a pharmaceutically acceptable excipient to obtain wet granules; drying the wet granules to obtain dried granules; milling the dried granules to obtain milled granules; mixing the milled granules with a disintegrant to obtain the composition; mixing the composition with a lubricant to obtain a tableting blend; and compressing the tableting blend to obtain a colchicine tablet.

Also disclosed herein are methods of making ultrapure colchicine.

In an embodiment, the method comprises subjecting colchicine comprising more than about 3.0% total impurities to column chromatography to obtain a colchicine concentrate, distilling the colchicine concentrate to obtain a colchicine distillate, and crystallizing ultrapure colchicine from the colchicine distillate; wherein the ultrapure colchicine comprises no more than about 3.0% total impurities.

In another embodiment, the method comprises subjecting colchicine comprising more than about 3.0% total impurities to neutral alumina column chromatography to obtain a colchicine concentrate; distilling the colchicine concentrate with ethyl acetate to obtain a colchicine distillate; and crystallizing ultrapure colchicine from the colchicine distillate in ethyl acetate; wherein the ultrapure colchicine comprises no more than about 3.0% total impurities.

In still another embodiment, the method comprises subjecting colchicine comprising more than about 3.0% total impurities to neutral alumina column chromatography to obtain a colchicine concentrate; distilling the colchicine concentrate with ethyl acetate to obtain a colchicine distillate; crystallizing a purified colchicine from the colchicine distillate in ethyl acetate; washing the purified colchicine with ethyl acetate to obtain a washed purified colchicine; and drying the washed purified colchicine to obtain ultrapure colchicine, wherein the ultrapure colchicine comprises no more than about 3.0% total impurities.

Also disclosed are methods of treating a patient with the colchicine compositions.

In an embodiment, the method comprises administering a dosing regimen to a patient having an acute gouty arthritis attack, wherein the dosing regimen consists of two colchicine dosage forms at the onset of the acute gouty arthritis attack,

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followed by one colchicine dosage form in about one hour, wherein a colchicine dosage form comprises about 0.6 mgA colchicine.

In an embodiment, the method comprises administering less than about 2 mg of colchicine to a patient over a period of about one hour, wherein the patient is experiencing an acute gouty arthritis attack.

In an embodiment, the method comprises administering to a human experiencing an acute gouty arthritis attack a colchicine composition, wherein the composition is effective to provide a colchicine plasma concentration profile having an area under the plasma colchicine concentration curve from time 0 to infinity (AUC<sub>0- $\infty$</sub> ) of about 34.2 ng-hr/mL to about 74.1 ng-hr/mL, an area under the plasma colchicine concentration curve from time 0 to time t (AUC<sub>0-t</sub>) of about 28.8 ng-hr/mL to about 58.9 ng-hr/mL, or a maximum plasma colchicine concentration (Cmax) of about 3.2 ng/mL to about 11.4 ng/mL for a maximum total dose of about 1.8 mg colchicine.

In an embodiment, the method comprises administering a dosing regimen to a patient having an acute gouty arthritis attack, wherein the dosing regimen consists of two colchicine dosage forms at the onset of the acute gouty arthritis attack, followed by one colchicine dosage form in about one hour, wherein a colchicine dosage form comprises about 0.6 mgA colchicine, wherein the dosing regimen is effective to provide an area under the plasma colchicine concentration curve from time 0 to infinity (AUC<sub>0- $\infty$</sub> ) of about 34.2 ng-hr/mL to about 74.1 ng-hr/mL, an area under the plasma colchicine concentration curve from time 0 to time t (AUC<sub>0-t</sub>) of about 28.8 ng-hr/mL to about 58.9 ng-hr/mL, or a maximum plasma colchicine concentration (Cmax) of about 3.2 ng/mL to about 11.4 ng/mL.

In an embodiment, the method comprises administering a dosing regimen to a patient having an acute gouty arthritis attack, wherein the dosing regimen consists of two colchicine dosage forms at the onset of the acute gouty arthritis attack, followed by one colchicine dosage form in about one hour, wherein a colchicine dosage form comprises about 0.6 mgA colchicine, wherein the dosing regimen is effective to provide a colchicine plasma concentration profile which has a maximum plasma colchicine concentration (Cmax) which is at least 80% of plasma Cmax provided by a dosing regimen of two dosage forms, followed by one dosage form about every hour later for 6 hours.

In an embodiment, the method comprises administering a dosing regimen to a patient having an acute gouty arthritis attack, wherein the dosing regimen consists of two colchicine dosage forms at the onset of the acute gouty arthritis attack, followed by one colchicine dosage form in about one hour, wherein a colchicine dosage form comprises about 0.6 mgA colchicine, wherein the odds of a patient being a responder to the dosing regimen are not statistically different from the odds of being a responder to a second dosing regimen consisting of two colchicine dosage forms at the onset of the acute gouty arthritis attack, followed by one colchicine dosage form every hour for 6 hours, wherein a responder is a patient obtaining a  $\geq 50\%$  improvement in pain at 24 hours after the first dose, without taking an additional active agent for reducing pain of the acute gouty arthritis attack.

In an embodiment, the method comprises administering a dosing regimen to a patient having an acute gouty arthritis attack, wherein the dosing regimen consists of two colchicine dosage forms at the onset of the acute gouty arthritis attack, followed by one colchicine dosage form in about one hour, wherein a colchicine dosage form comprises about 0.6 mgA colchicine, wherein in a randomized, placebo-controlled

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study of the dosing regimen in patients with an acute gouty arthritis attack, the fraction of patients that experienced a given % improvement in pain at 24 hrs after first dose is shown in FIG. 1.

These and other embodiments, advantages and features of the present invention become clear when detailed description and examples are provided in subsequent sections.

#### BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows the fraction of all patients improved at 24 hrs post-first dose of colchicine, regardless of pain rescue, as a function of the percent improvement in pain determined in the study of Example 3.

#### DETAILED DESCRIPTION

Disclosed herein are compositions comprising ultrapure colchicine and a pharmaceutically acceptable excipient. Herein, "ultrapure colchicine" means colchicine comprising no more than about 3.0% of total impurities, measured chromatographically as described below, specifically the ultrapure colchicine comprises no more than about 2.0% of total impurities, more specifically no more than about 1.0% of total impurities, or even more specifically no more than about 0.5% of total impurities. In some embodiments, the ultrapure colchicine comprises no more than about 0.10% of N-deacetyl-N-formyl colchicine, measured chromatographically. In some embodiments, the ultrapure colchicine is purified from a botanical source. Methods of making ultrapure colchicine and the compositions comprising the ultrapure colchicine, methods of treating various conditions using the compositions. Dosing regimens are also disclosed.

Not wishing to be bound by theory, it is postulated that the properties of colchicine as an antimitotic agent (e.g. its tubulin binding properties) or its effects on Pgp transporter properties provide the therapeutic effects of colchicine described herein. The methods described herein therefore also contemplate the use of an antimitotic agent with at least one pharmaceutically acceptable excipient. An antimitotic agent can be a drug that prevents or inhibits mitosis, or cell division.

In the specification and claims that follow, references will be made to a number of terms which shall be defined to have the following meaning.

The terms "a" and "an" do not denote a limitation of quantity, but rather denote the presence of at least one of the referenced item. The term "or" means "and/or". The terms "comprising", "having", "including", and "containing" are to be construed as open-ended terms (i.e., meaning "including, but not limited to") unless otherwise noted.

An "active agent" means a compound (including for example, colchicine), element, or mixture that when administered to a patient, alone or in combination with another compound, element, or mixture, confers, directly or indirectly, a physiological effect on the patient. The indirect physiological effect may occur via a metabolite or other indirect mechanism. When the active agent is a compound, then salts, solvates (including hydrates), and co-crystals of the free compound or salt, crystalline forms, non-crystalline forms, and any polymorphs of the compound are contemplated herein. Compounds may contain one or more asymmetric elements such as stereogenic centers, stereogenic axes and the like, e.g., asymmetric carbon atoms, so that the compounds can exist in different stereoisomeric forms. These compounds can be, for example, racemates or optically active forms. For compounds with two or more asymmetric elements, these compounds can additionally be mixtures of diastereomers.

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For compounds having asymmetric centers, all optical isomers in pure form and mixtures thereof are encompassed. In addition, compounds with carbon-carbon double bonds may occur in Z- and E-forms, with all isomeric forms of the compounds. In these situations, the single enantiomers, i.e., optically active forms can be obtained by asymmetric synthesis, synthesis from optically pure precursors, or by resolution of the racemates. Resolution of the racemates can also be accomplished, for example, by conventional methods such as crystallization in the presence of a resolving agent, or chromatography, using, for example, a chiral HPLC column. All forms are contemplated herein regardless of the methods used to obtain them.

"Bioavailability" means the extent or rate at which an active agent is absorbed into a living system or is made available at the site of physiological activity. For active agents that are intended to be absorbed into the bloodstream, bioavailability data for a given formulation may provide an estimate of the relative fraction of the administered dose that is absorbed into the systemic circulation. "Bioavailability" can be characterized by one or more pharmacokinetic parameters.

"Bioequivalence" or "equivalent bioavailability" means the absence of a significant difference in the rate or extent to which the active agent in pharmaceutical equivalents or pharmaceutical alternatives is absorbed into a living system or is made available at the site of physiological activity or the absence of a significant difference in the rate or extent to which the active agent in a pharmaceutical composition is absorbed into a living system or is made available at the site of physiological activity when administered by two different methods (e.g., dosing under non-fasted versus fasted conditions). Bioequivalence can be determined by comparing in vitro dissolution testing data for two dosage forms or two dosing conditions or by comparing pharmacokinetic parameters for two dosage forms or two dosing conditions.

In some embodiments, two products (e.g. an inventive composition and COL-PROBENECID®) or two methods (e.g., dosing under fed (non-fasted) versus fasted conditions) are bioequivalent if the ratio of the geometric mean of logarithmic transformed  $AUC_{0-\infty}$ ,  $AUC_{0-t}$ , or  $C_{max}$  for the two products or two methods is about 0.80 to about 1.25; specifically if the 90% Confidence Interval (CI) limit for the ratio of the geometric mean of logarithmic transformed  $AUC_{0-\infty}$ ,  $AUC_{0-t}$ , or  $C_{max}$  for the two products or two methods is about 0.80 to about 1.25; more specifically if the ratios of the geometric mean of logarithmic transformed  $AUC_{0-\infty}$ ,  $AUC_{0-t}$ , and  $C_{max}$  for the two products or two methods are about 0.80 to about 1.25; yet more specifically if the 90% Confidence Interval (CI) limits for the ratios of the geometric mean of logarithmic transformed  $AUC_{0-\infty}$ ,  $AUC_{0-t}$ , and  $C_{max}$  for the two products or two methods are about 0.80 to about 1.25.

"Colchicine therapy" refers to medical treatment of a symptom, disorder, or condition by administration of colchicine. Colchicine therapy can be considered optimal when effective plasma levels are reached when required. In addition, peak plasma values ( $C_{max}$ ) should be as low as possible so as to reduce the incidence and severity of possible side effects.

"Conventional colchicine" means colchicine comprising more than 3% but no more than about 5.0% total impurities, measured chromatographically as described below, and comprising more than about 0.010% of N-deacetyl-N-formyl colchicine.

A "dosage form" means a unit of administration of an active agent. Examples of dosage forms include tablets, cap-

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sules, injections, suspensions, liquids, emulsions, creams, ointments, suppositories, inhalable forms, transdermal forms, and the like.

"Dosing regimen" means the dose of an active agent taken at a first time by a patient and the interval (time or symptomatic) at which any subsequent doses of the active agent are taken by the patient. The additional doses of the active agent can be different from the dose taken at the first time.

A "dose" means the measured quantity of an active agent to be taken at one time by a patient.

"Efficacy" means the ability of an active agent administered to a patient to produce a therapeutic effect in the patient.

As used herein, the term "mgA" refers to milligrams of the active colchicine, or the free base of colchicine, after compensating for the potency of the batch of colchicine (i.e., after compensating for impurities, including solvents, and salts in the colchicine). For example, 0.612 mg of an ultrapure colchicine free base having a total impurity of 2 wt % (thus a purity of 98 wt %) contains 0.6 mgA ( $0.612 \text{ mg} \times 0.98 = 0.6 \text{ mgA}$ ) of colchicine.

An "oral dosage form" means a unit dosage form for oral administration.

A "patient" means a human or non-human animal in need of medical treatment. Medical treatment can include treatment of an existing condition, such as a disease or disorder, prophylactic or preventative treatment, or diagnostic treatment. In some embodiments the patient is a human patient.

"Pharmaceutically acceptable" means that which is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes that which is acceptable for veterinary use as well as human pharmaceutical use.

"Pharmaceutically acceptable salts" includes derivatives of colchicine, wherein the colchicine is modified by making acid or base addition salts thereof, and further refers to pharmaceutically acceptable solvates, including hydrates, and co-crystals of such compounds and such salts. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid addition salts of basic residues such as amines; alkali or organic acid addition salts of acidic residues; and the like, and combinations comprising one or more of the foregoing salts. The pharmaceutically acceptable salts include non-toxic salts and the quaternary ammonium salts of the colchicine. For example, non-toxic acid salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; other acceptable inorganic salts include metal salts such as sodium salt, potassium salt, cesium salt, and the like; and alkaline earth metal salts, such as calcium salt, magnesium salt, and the like, and combinations comprising one or more of the foregoing salts. Pharmaceutically acceptable organic salts includes salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pantoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, mesylic, esylic, besylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic,  $\text{HOOC}-(\text{CH}_2)_n-\text{COOH}$  where  $n$  is 0-4, and the like; organic amine salts such as triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt,  $\text{N,N}'$ -dibenzylethylenediamine salt, and the like; and amino acid salts such as arginate, aspartate, glutamate, and the like; and combinations comprising one or more of the foregoing salts; organic amine salts such as triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt,  $\text{N,N}'$ -dibenzylethylenediamine salt, and the like; and amino acid salts such as arginate, aspartate, glutamate, and the like;

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and combinations comprising one or more of the foregoing salts. All forms of such derivatives of colchicine are contemplated herein, including all crystalline, amorphous, and polymorph forms. Specific colchicine salts include colchicine hydrochloride, colchicine dihydrochloride, and co-crystals, hydrates or solvates thereof.

"Pharmacokinetic parameters" describe the in vivo characteristics of an active agent (or a metabolite or a surrogate marker for the active agent) over time, such as plasma concentration ( $C$ ),  $C_{max}$ ,  $C_n$ ,  $C_{24}$ ,  $T_{max}$ , and AUC. " $C_{max}$ " is the measured plasma concentration of the active agent at the point of maximum, or peak, concentration. " $C_{min}$ " is the measured plasma concentration of the active agent at the point of minimum concentration. " $C_n$ " is the measured plasma concentration of the active agent at about  $n$  hours after administration. " $C_{24}$ " is the measured plasma concentration of the active agent at about 24 hours after administration. The term " $T_{max}$ " refers to the time at which the measured plasma concentration of the active agent is the highest after administration of the active agent. "AUC" is the area under the curve of a graph of the measured plasma concentration of an active agent vs. time, measured from one time point to another time point. For example  $\text{AUC}_{0-t}$  is the area under the curve of plasma concentration versus time from time 0 to time  $t$ , where  $t$  can be the last time point with measurable plasma concentration for an individual formulation. The  $\text{AUC}_{0-\infty}$  or  $\text{AUC}_{0-\text{INF}}$  is the calculated area under the curve of plasma concentration versus time from time 0 to time infinity. In steady-state studies,  $\text{AUC}_{0-\tau}$  is the area under the curve of plasma concentration over the dosing interval (i.e., from time 0 to time  $\tau$  (tau), where tau is the length of the dosing interval. Other pharmacokinetic parameters are the parameter  $K_e$  or  $K_{el}$ , the terminal elimination rate constant calculated from a semi-log plot of the plasma concentration versus time curve;  $t_{1/2}$  the terminal elimination half-life, calculated as  $0.693/K_{el}$ ;  $\text{CL}/F$  denotes the apparent total body clearance after administration, calculated as  $\text{Total Dose}/\text{Total AUC}_\infty$ ; and  $V_{\text{area}}/F$  denotes the apparent total volume of distribution after administration, calculated as  $\text{Total Dose}/(\text{Total AUC}_\infty \times K_{el})$ .

"Adverse event" means any untoward medical occurrence in a patient administered an active agent and which does not necessarily have to have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of the active agent, whether or not considered related to the active agent.

"Side effect" means a secondary effect resulting from taking an active agent. The secondary effect can be a negative (unfavorable) effect (i.e., an adverse side effect) or a positive (favorable) effect.

The most frequently reported adverse side effects to colchicine therapy are gastrointestinal, specifically diarrhea; abdominal pain with cramps; nausea; and vomiting. Less frequently or rarely reported adverse side effects associated with colchicine therapy include anorexia, agranulocytosis, allergic dermatitis, allergic reactions, alopecia, angioedema, aplastic anemia, bone marrow depression, myopathy, neuropathy, skin rash, thrombocytopenic disorder, and urticaria.

Determining that a patient experiences an adverse side effect can be performed by obtaining information from the patient regarding onset of certain symptoms which may be indicative of the adverse side effect, results of diagnostic tests indicative of the adverse side effect, and the like.

Ultrapure colchicine comprising low levels of individual impurities or total impurities is highly desirable as compared to conventionally available forms of colchicine. Currently,

commercially available forms of colchicine often comprise high levels of impurities. Depending on the source or the preparation process, colchicine may comprise some or all of the common impurities shown in Table 1.

TABLE 1

Common Impurities	Chemical Name	Other common name
Impurity A	N-[(7S,12aS)-1,2,3,10-tetramethoxy-9-oxo-5,6,7,9-tetrahydrobenzo[a]heptalen-7-yl]formamide	N-deacetyl-N-formyl colchicine
Impurity B	(-)-N-[(7S,12aR)-1,2,3,10-tetramethoxy-9-oxo-5,6,7,9-tetrahydrobenzo[a]heptalen-7-yl]-acetamide	Conformational isomer
Impurity C	N-[(7S,7bR,10aS)-1,2,3,9-tetramethoxy-8-oxo-5,6,7,7b,8,10a-hexahydrobenzo[a]cyclopenta[3,4]cyclobuta[1,2-c]cyclohepten-7-yl]-acetamide	β-Lumicolchicine
Impurity D	N-[(7S,12aS)-3-(β-D-glucopyranosyloxy)-1,2,10-trimethoxy-9-oxo-5,6,7,9-tetrahydrobenzo[a]heptalen-7-yl]-acetamide	Colchicoside
Impurity E	N-[(7S,12aS)-3-hydroxy-1,2,10-trimethoxy-9-oxo-5,6,7,9-tetrahydrobenzo[a]heptalen-7-yl]-acetamide	3-O-demethyl colchicine
Impurity F	N-[(7S,12aS)-10-hydroxy-1,2,3-trimethoxy-9-oxo-5,6,7,9-tetrahydrobenzo[a]heptalen-7-yl]acetamide	Colchicine

In addition to the common impurities listed above, colchicine may also comprise N-[(7S,12aS)-2-hydroxy-1,3,10-trimethoxy-9-oxo-5,6,7,9-tetrahydrobenzo[a]heptalen-7-yl]-acetamide (“2-O-demethyl colchicine”) impurity. Some analytical methods cannot differentiate 2-O-demethyl colchicine from 3-O-demethyl colchicine.

In addition to the common impurities listed above, colchicine may also comprise other structurally unidentified impurities. In fact, conventional forms of colchicine may comprise as much as 5% of total impurities, determined chromatographically as described below. Such high levels of impurities in conventional colchicine pose several problems. The impurities may cause side effects in patients taking dosage forms comprising conventional colchicine. For example, N-deacetyl-N-formyl-colchicine (Impurity A, also known as Gloriosine) is tumorigenic and has been studied as an anticancer agent. Therefore reduction in the level of N-deacetyl-N-formyl colchicine found in convention colchicine is highly desirable. Additionally, high levels of impurities can also pose a regulatory challenge for pharmaceutical companies using conventional colchicine in products. For a pharmaceutical product comprising an active agent, the United States Food and Drug Administration (FDA) requires “qualification” or toxicity information for any impurity that is greater than the International Conference on Harmonization (ICH) qualification threshold of 0.15% per individual impurity in the active agent substance or 1.0% in the dosage form. Thus, there is a regulatory benefit for a pharmaceutical company to market pharmaceutical products comprising active agents comprising low levels of individual impurities or total impurities in the active agent substance as well as in the dosage form. As a result, for a pharmaceutical composition comprising colchicine, it is in the best interest of both the pharmaceutical company and the patient that impurities be minimized, if possible, in the colchicine and in colchicine compositions or dosage forms.

The ultrapure colchicine disclosed herein comprises no more than (NMT) about 3.0%; specifically NMT about 2.0%, or more specifically, NMT about 1.0%, or even more specifically NMT about 0.5% of total impurities. In one embodiment, “total impurities” includes the common impurities,

Impurities A through F, as well as all structurally unidentified impurities eluting within 1.5 times the retention time of colchicine using an HPLC method as described in more detail below. In another embodiment, other HPLC and HPLC methods, for example, as described in more detail below, can be used to quantify the level of total impurities.

The ultrapure colchicine may also comprise low levels of individual impurities. In one embodiment, the ultrapure colchicine comprises NMT about 2.0%, specifically NMT about 1.5%; more specifically NMT about 1.0%; or yet more specifically, NMT about 0.5%, or even more specifically, NMT about 0.15%, or still more specifically, NMT about 0.10%, of any individual impurity. The impurity can be Impurity A, Impurity B, Impurity C, Impurity D, Impurity E, Impurity F, or an unidentified impurity.

In an embodiment, the ultrapure colchicine comprises no more than (NMT) about 3.0% total impurities and NMT about 0.10% N-deacetyl-N-formyl colchicine.

In another embodiment, the ultrapure colchicine comprises NMT about 3.0% total impurities; NMT about 0.1% per individual impurity of Impurity A, Impurity C, Impurity D, and Impurity E; NMT about 0.15% Impurity F; and NMT about 2.0% of Impurity B.

Not wishing to be bound by theory, it is postulated that the conformational isomer, Impurity B, is in equilibrium with the active colchicine such that even after purification of the colchicine to about 0.5% Impurity B, the purified colchicine re-equilibrates to a level of Impurity B around about 1% to about 1.3%.

The level of an individual impurity or of total impurities in colchicine may be determined by any suitable analytical method known in the art. In one embodiment, the impurity levels are determined using a high performance liquid chromatography (HPLC) assay, for example, the HPLC method described in the Colchicine Official Monograph USP30/NF25, herein fully incorporated by reference.

Exemplary conditions for HPLC or ultra performance liquid chromatography (HPLC) assays that can be used for the impurity analysis of colchicine or of a colchicine pharmaceutical product are listed in Table 2.

TABLE 2

Exemplary HPLC Conditions For Colchicine Purity Analysis			
	USP30/NF25 Colchicine Official Monograph Method	HPLC Method	UPLC Method
Mobile phase	0.5 Molar KH <sub>2</sub> PO <sub>4</sub> in Methanol:Water (65:45, v:v), pH adjusted to 5.5 with H <sub>3</sub> PO <sub>4</sub>	pH 7.2 10 mM Phosphate Buffer:methanol (MeOH) Gradient	pH 4.5 Ammonium Acetate Buffer:MeOH Gradient
Column	Octylsilyl silica gel, 4.6 mm × 25 cm, 5 micron	Zorbax SBC(18) 4.6 × 250 mm	Acquity GEH C18 2.1 × 100 mm, 1.7 um
Flow rate	1.0 mL/min	1.0 mL/min	0.25 mL/min
Column Ambient		Ambient	30 C. +/- 2 C.
Temp			
Detection	254 nanometers (nm)	246 nm	246 nm
Injection volume	20 microliters (uL)	75 uL	7 uL
Sample Conc.	0.006 mg/mL	0.120 mg/ml	0.012 mg/ml
Run time	15 minutes (min)	46 min	25 min

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When using one of the above HPLC conditions in Table 2 for colchicine purity analysis, the relative retention time (RRT) of an impurity can be calculated by the following formula:

$$\text{RRT of an impurity} = \text{RT of the impurity} / \text{RT of colchicine},$$

where RT stands for retention time of the impurity or the colchicine at the particular conditions used in the assay.

In one embodiment, using the HPLC method in Table 2, the retention time (RT) of colchicine is about 7 minutes and the relative retention times (RRTs) of the common impurities eluting within 1.5 times the retention time for colchicine are listed in Table 2A:

TABLE 2A

Relative Retention Times (RRTs) of the Common Impurities	
Impurity ID	RRT
N-deacetyl-N-formyl colchicine - Impurity A	0.94
Conformational isomer - Impurity B	0.8
$\beta$ -Lumicolchicine - Impurity C	1.2
Colchicoside - Impurity D	0.4
3-O-demethyl colchicine - Impurity E	0.7

In one embodiment, the percent of a particular impurity is calculated by dividing the response (peak area) of the impurity peak by the sum of all responses (total peak area of all peaks, including the colchicine peak and all common and unidentified impurity peaks) eluting within 1.5 times the retention time for colchicine in the HPLC assay and multiplying the result by 100%.

In one embodiment, the level (%) of total impurities is calculated by dividing the sum of responses of any peaks other than that due to colchicine eluting within 1.5 times the retention time for colchicine by the sum of all responses eluting in the HPLC assay and multiplying the result by 100%.

An additional HPLC method for determining the level of impurities other than Impurity F in colchicine or in colchicine pharmaceutical products has been developed and validated for use as an alternative to the methods in Table 2 above. The method is shown in Table 3A below.

TABLE 3A

Quantitative HPLC Method for determining all impurities other than impurity F in colchicine and colchicine pharmaceutical products.	
Quantitative HPLC Method for colchicine and colchicine products.	
Mobile phase	pH 4.5 Ammonium Acetate Buffer: methanol Gradient
Column	Waters XBridge C18, 250 mm $\times$ 4.6 mm, 5 $\mu$ m particle size
Flow rate	0.9 mL/min
Column Temp	10 $\pm$ 3.5 C. (for column)/10 $\pm$ 2 C. (for sample)
Detection	246 nm
Injection volume	75 $\mu$ L
Sample Conc.	0.16 mg/ml
Run time	60 min

In the quantitative HPLC method of Table 3A, the retention time (RT) of colchicine is about 24 minutes and the relative retention times (RRTs) of the common impurities for colchicine are listed in Table 3B:

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TABLE 3B

Relative Retention Times (RRTs) of the Common Impurities	
Impurity ID	RRT
N-deacetyl-N-formyl colchicine - Impurity A	0.93
Conformational isomer - Impurity B	0.82
$\beta$ -Lumicolchicine - Impurity C	1.76
Colchicoside - Impurity D	0.18
3-O-demethyl colchicine - Impurity E	0.52
2-O-demethyl colchicine	0.54
Gamma-Lumicolchicine	1.37

The percentage of individual impurities in the sample solution is calculated as follows:

$$\% \text{ Impurity} = \frac{r_i}{r_s} \times \frac{W_s(\text{mg})}{100 \text{ mL}} \times \frac{6.0 \text{ mL}}{100 \text{ mL}} \times \frac{2.0 \text{ mL}}{100 \text{ mL}} \times P \times \left( \frac{100 - \% RS_s - \% W_s}{100} \right) \times \frac{200 \text{ mL}}{SW(\text{mg}) \times \left( \frac{100 - \% RS_s - \% W_s}{100} \right)} \times \frac{100\%}{RRF}$$

Where:

$r_s$  = The area response of the Colchicine peak in the Working Standard Solution.

$r_i$  = The area response of the impurity peak in the Sample Solution

P = % Purity of the Colchicine Reference Standard divided by 100%.

SW = Weight of Sample taken for Sample Preparation

$W_s$  = Weight of Colchicine in the Stock Standard Solution

RRF = Relative Response Factor for specified and unspecified impurities, 1.0

%  $RS_{s/u}$  = Percent of Residual Solvents in the Colchicine Standard/Sample

%  $W_{s/u}$  = % Water in the Colchicine Standard/Sample

To date, the impurity colchicine (Impurity F or 10-O-Demethyl Colchicine "10-DMC") has been typically analyzed by a qualitative calorimetric test described in the Colchicine Official Monograph USP30/NF25 using ferric chloride solution, rather than chromatographically. The standard for acceptable levels of Impurity F has been absence of production of a definite green color in a solution of colchicine.

However, a chromatographic method has been developed for the determination of Impurity F (Colchicine or 10-O-Demethyl Colchicine "10-DMC"). The chromatographic conditions are as follows:

TABLE 3C

HPLC parameters for Colchicine determination	
HPLC System:	HPLC equipped with a pump, auto sampler, variable wavelength detector and a suitable data acquisition system.
Column:	Phenomenex Gemini C18 150 mm $\times$ 4.6 mm 5 $\mu$ m, 110 Å
Detection:	245 nm
Flow Rate:	About 1.5 mL/min
Injection Volume:	50 $\mu$ L
Temperature:	Column: 10° C. $\pm$ 3.5° C. Sample: 5° C. $\pm$ 2° C.
Needle Rinse Setting:	Double
Needle Wash:	Water:Acetonitrile (50:50)
Digital Filter Response:	1.0

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TABLE 3C-continued

HPLC parameters for Colchicine determination	
Sampling Rate:	5.0
Resolution:	1.2
Mobile Phase:	pH 4.5 Buffer Solution:Acetonitrile (75:25)
Run Time:	About 7 minutes for Standard
	About 20 minutes for first Blank and Samples

The LQL level for 10-DMC in this method is 0.776304  $\mu\text{g/mL}$ . The amount of 10-DMC expressed in percent of Colchicine is calculated as follows:

$$\% \text{ Purity} = \frac{r_i}{r_s} \times \frac{W_s(\text{mg}) \times P}{400 \text{ mL}} \times \left( \frac{100 - \% RS_s - \% W_s}{100} \right) \times \frac{3.0 \text{ mL}}{100 \text{ mL}} \times \frac{50 \text{ mL}}{W_u(\text{mg})} \times \left( \frac{100 - \% RS_u - \% W_u}{100} \right) \times \frac{100\%}{RRF}$$

Where:

$r_i$ =The peak area response of 10-DMC in the Sample Solution

$r_s$ =The peak area response of Colchicine in the Working Standard Solution

$W_s$ =The weight of Colchicine in the Stock Standard Preparation

$W_u$ =The weight of Colchicine in the Sample Preparation

$P$ =Standard purity factor expressed as labeled (% Purity/100)

$\% RS_{s/u}$ =Percent of Residual Solvents in the Colchicine Standard/Sample

$\% W_{s/u}$ =% Water in the Colchicine Standard/Sample

$RRF$ =Relative response factor for 10-DMC=0.88

Ultrapure colchicine may be obtained by various purification methods starting from colchicine-containing botanical extracts, conventional colchicine, or other partially-purified forms of colchicine. In some embodiments, the colchicine is purified from a botanical source. The botanical source can be any capable of providing colchicine, conventional or ultrapure, in quantities suitable for commercial pharmaceutical product manufacture

The literature from 1884-1997 on methods of isolation and purification of colchicine from various botanic sources, including for example *C. autumnale* corms or leaves and species of *Gloriosa* has been reviewed. (Kiselev & Yavich, 1991, "METHODS OF ISOLATING ALKALOIDS OF THE COLCHICINE SERIES"; Plenum Publishing Co., English translation of article from Khimiya Prirodnykh Soedinenii, No. 5, pp. 592-600, September-October, 1990.). Kiselev & Yavich also review reports in the literature of impurities detected in colchicine stored for various times, as follows. In an article published in 1944 it was reported that chromatography of colchicine corresponding to the requirements of the USP of that time showed the presence of 5% of impurities and various amount of individual impurities. An article published in 1952 reported that colchicine meeting the requirements of the USP contained about 4% of 3-demethylcolchicine. A 1953 article reported 1.5% of N-formyldeacetylcolchicine isolated and the presence of other accompanying alkaloids in a pharmacopeial sample of colchicine. An investigation of a commercial sample by high-resolution liquid chromatography, published in 1986, reported finding 93.4% of colchicine, 2.9% of N-formyldeacetylcolchicine, 1.8% of 17-hydroxycolchicine, and 0.84% of an unknown substance.

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Walaszik et al. describes a process of incorporating carbon 14 into *C. autumnale* plants and isolating radioactive colchicine from the radioactive plants (See Walaszik et al., Science (1952) 116:225-227). However, the level of impurities in the isolated radioactive colchicine is not disclosed.

The purification methods disclosed herein produce ultrapure colchicine comprising very low levels of total impurities or individual impurities. In one embodiment, ultrapure colchicine may be obtained from conventional colchicine obtained commercially or produced using solvent extraction of appropriate botanic material as described in more detail below.

In one embodiment, conventional colchicine may be obtained by isolating colchicine from a colchicine chloroform extract. The extract is washed with a mixture of purified water, sodium hydroxide solution, sodium chloride solution and acetic acid. The washed extract is filtered and the resulting concentrate is distilled in two steps, first using methanol, and second using ethyl acetate. The resulting distillate is crystallized. Ethyl acetate can be used to isolate and wash the crystallized colchicine, which is then dried to yield conventional colchicine. The conventional colchicine comprises more than about 3.0% but no more than 5% total impurities.

The conventional colchicine may be used directly in a colchicine composition comprising a pharmaceutically acceptable excipient. It may also be used for further purification to obtain ultrapure forms of colchicine.

In one embodiment of a method of making ultrapure colchicine, the conventional colchicine may be subjected to column chromatography to obtain a purified colchicine concentrate, distilling the purified colchicine concentrate to obtain a colchicine distillate, and crystallizing ultrapure colchicine from the colchicine distillate. The method can further comprise washing the crystallized ultrapure colchicine with a solvent and drying. The ultrapure colchicine comprises no more than about 3.0% of total impurities.

In one embodiment, the column chromatography is carried out using methylene chloride as solvent on a column of neutral alumina. Other solvents or chromatographic media may be used, provided that impurities are removed from the conventional colchicine to the desired level. In another embodiment, distillation of the purified colchicine concentrate is carried out using ethyl acetate. Other organic solvents can be used, provided that impurities are removed from the purified colchicine concentrate. In yet another embodiment, the solvent used to wash the crystallized ultrapure colchicine is ethyl acetate.

In another embodiment, a method of making ultrapure colchicine comprises subjecting colchicine comprising more than about 3.0% total impurities to neutral alumina column chromatography to obtain a colchicine concentrate; distilling the colchicine concentrate with ethyl acetate to obtain a colchicine distillate; crystallizing a purified colchicine from the colchicine distillate in ethyl acetate; washing the purified colchicine with ethyl acetate to obtain a washed purified colchicine; and drying the washed purified colchicine to obtain ultrapure colchicine, wherein the ultrapure colchicine comprises no more than about 3.0% total impurities.

In one embodiment, the ultrapure colchicine obtained in any of the above methods comprises no more than about 2.0% total impurities. In another embodiment, the ultrapure colchicine comprises no more than about 1.5% total impurities. In another embodiment, the ultrapure colchicine comprises no more than about 1.0% total impurities. In another embodiment, the ultrapure colchicine comprises no more than about 0.5% total impurities. In yet another embodiment, the ultrapure colchicine comprises no more than about 0.5% per indi-

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vidual impurity of Impurity A, Impurity B, Impurity C, Impurity D, Impurity E, or Impurity F. In still another embodiment, the ultrapure colchicine comprises no more than about 0.15% per individual impurity of Impurity A, Impurity C, Impurity D, Impurity E, or Impurity F. In another embodiment, the ultrapure colchicine comprises no more than about 1.0% of total unidentified impurities. In yet another embodiment, the ultrapure colchicine comprises no more than about 0.5% of total unidentified impurities. In yet another embodiment, the ultrapure colchicine comprises no more than 1.0% of Impurity B, and no more than 0.1% per individual impurity of any of Impurity A, Impurity C, Impurity D, Impurity E, and Impurity F.

The above methods of making ultrapure colchicine are only examples of suitable methods for its preparation.

The colchicine compositions disclosed herein comprise colchicine and a pharmaceutically acceptable excipient. In one embodiment, the colchicine composition comprises 0.1 wt % to 10 wt % colchicine, specifically 0.1 wt % to 5 wt % colchicine. In one embodiment, the colchicine in the colchicine compositions is ultrapure colchicine. The compositions comprising ultrapure colchicine are stable and provide enhanced safety to patients taking the compositions because the patients are ingesting fewer impurities. In particular, the colchicine compositions contain substantially lower levels of the tumorigenic compound N-deacetyl-N-formyl colchicine.

The pharmaceutically acceptable excipient in the colchicine composition may be a filler (or diluent), a binder, a disintegrant, a lubricant, or a combination comprising two or more of the foregoing excipients.

In one embodiment, the pharmaceutically acceptable excipient comprises a filler. Exemplary fillers may be one or more compounds which are capable of providing compactability and good flow. Exemplary fillers include microcrystalline cellulose, starch, lactose, sucrose, glucose, mannitol, maltodextrin, sorbitol, dextrose, silicic acid, dibasic calcium phosphate, or a combination comprising at least one of the foregoing fillers. Exemplary lactose forms include lactose monohydrate, NF (Fast Flo), lactose spray-dried monohydrate, and lactose anhydrous. Exemplary microcrystalline cellulose (MCC) include, for example, AVICEL® PH101 and AVICELL® PH102, which are commercially available from FMC Biopolymer, Philadelphia, Pa. Exemplary dibasic calcium phosphates include dihydrated and anhydrous dibasic calcium phosphates. In one embodiment, the filler is a combination of microcrystalline cellulose and lactose monohydrate, NF (fast flo).

When present, the amount of the filler in the composition may be about 10 wt % to about 99 wt %, or more specifically, about 30 wt % to about 90 wt %, or even more specifically, about 50 wt % to about 90 wt %, or still more specifically, about 70 wt % to about 85 wt %, based on the total weight of the composition. In one embodiment, the total amount of the filler is about 82 wt %, based on the total weight of the composition.

In one embodiment, the pharmaceutically acceptable excipient comprises a binder. Binders may be used to impart cohesive qualities to a formulation, for example, a tablet formulation, and thus ensure that the tablet remains intact after compaction. Exemplary binders include starches (for example, Starch 1500® or pregelatinized starch), alginates, gelatin, carboxymethylcellulose, sugars (for example, sucrose, glucose, dextrose, and maltodextrin), polyethylene glycol, waxes, natural and synthetic gums, polyvinylpyrrolidone, and cellulosic polymers (for example, microcrystalline cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methyl cellulose, and hydroxyethyl cellulose) and

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combinations comprising one or more of the foregoing binders. In one embodiment, the binder is starch, or more specifically, pregelatinized starch.

When present, the amount of the binder may be about 10 wt % to about 99 wt %, or more specifically, about 10 wt % to about 50 wt %, or even more specifically, about 10 wt % to about 20 wt %, based on the total weight of the composition. In one embodiment, the amount of the binder is about 14 wt %, based on the total weight of the composition.

In another embodiment, the pharmaceutically acceptable excipient comprises a disintegrant. Disintegrants are used to facilitate disintegration or "breakup" of a composition, for example, a tablet, after administration. Exemplary disintegrants include sodium starch glycolate, sodium crosscarmellose (cross-linked carboxy methyl cellulose), crosslinked polyvinylpyrrolidone (PVP-XL), anhydrous calcium hydrogen phosphate, agar-agar, potato or tapioca starch, alginic acid, or a combination comprising one or more of the foregoing disintegrants.

When present, the disintegrant may be present in an amount of about 0.1 to 30 wt %, or more specifically, about 1 to 20 wt %, or even more specifically, about 1 to 10 wt %, based on the total weight of the composition. In one embodiment, the amount of the disintegrant is about 4.5 wt %, based on the total weight of the composition.

In another embodiment, the pharmaceutically acceptable excipient comprises a lubricant. Generally, a lubricant is added just before tableting, and is mixed with the rest of the composition for a minimum period of time to obtain good dispersal. Exemplary lubricants include magnesium stearate, calcium stearate, zinc stearate, stearic acid, talc, glyceryl behenate, polyethylene glycol, polyethylene glycol, polyethylene oxide, sodium lauryl sulfate, magnesium lauryl sulfate, sodium oleate, sodium stearyl fumarate, DL-leucine, colloidal silica, or a combination comprising one or more of the foregoing lubricants. In one embodiment, the lubricant is magnesium stearate, calcium stearate, or zinc stearate.

When present, the lubricant may be present in an amount of about 0.01 wt % to about 10 wt %, or more specifically, about 0.1 wt % to about 5 wt %, or even more specifically, about 0.1 wt % to about 1 wt %, based on the total weight of the composition. In one embodiment, the amount of the lubricant is about 0.6 wt %, based on the total weight of the composition.

If desired, the composition may optionally comprise small amounts of nontoxic auxiliary substances such as wetting or emulsifying agents, or pH buffering agents, for example, sodium acetate, sorbitan monolaurate, triethanolamine sodium acetate, triethanolamine oleate, sodium lauryl sulfate, dioctyl sodium sulfosuccinate, and polyoxyethylene sorbitan fatty acid esters.

In one embodiment, a composition comprises an ultrapure colchicine, wherein the ultrapure colchicine comprises no more than 3.0% of total impurities, a filler, a binder, and a disintegrant.

In another embodiment, a colchicine composition comprises about 0.6 mgA colchicine; about 14 mg pregelatinized starch; about 22 mg microcrystalline cellulose; about 4.3 mg sodium starch glycolate; about 0.6 mg magnesium stearate; and an amount of lactose monohydrate such that the colchicine composition has a total weight of about 100 mg. In one embodiment, the colchicine in the colchicine composition is ultrapure colchicine.

In an embodiment, a colchicine composition comprises colchicine; and a pharmaceutically acceptable excipient; wherein the colchicine composition comprises no more than about 3.5% total impurities, specifically no more than about

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3.0% total impurities, more specifically no more than about 2.0% total impurities, or yet more specifically no more than about 1.0% total impurities. In some of these embodiments, specific limitations on the levels of individual impurities are also met by the colchicine composition. In addition to containing no more than a particular maximum level of total impurities, the colchicine composition can comprise not more than about 0.42% Impurity A, Impurity C, Impurity D, Impurity E, or Impurity F, and not more than about 2.0% Impurity B; specifically not more than about 0.2% Impurity A, Impurity C, Impurity D, Impurity E, or Impurity F, and not more than about 1.5% Impurity B; and more specifically not more than about 0.15% Impurity A, Impurity C, Impurity D, Impurity E, or Impurity F, and not more than about 1.1% Impurity B. In one embodiment the colchicine composition comprises no more than 3.5% total impurities, no more than 0.42% Impurity A, and no more than 2.0% Impurity B. The pharmaceutically acceptable excipient can be one or more discussed previously herein.

In one embodiment, a colchicine composition comprises colchicine and a pharmaceutically acceptable excipient; wherein the colchicine composition comprises no more than about 3.5% total impurities. In some embodiments, the colchicine composition comprises ultrapure colchicine and total impurities in the ultrapure colchicine comprise no more than about 3.0%, or specifically no more than about 2.0%, or more specifically no more than about 1.5%, or yet more specifically, no more than about 1.0%. In addition to containing no more than a particular maximum level of total impurities, the ultrapure colchicine in the colchicine composition can comprise not more than about 0.15% Impurity A, Impurity C, Impurity D, Impurity E, or Impurity F, and not more than about 2.0% Impurity B; specifically not more than about 0.10% Impurity A, Impurity C, Impurity D, or Impurity E; not more than about 0.15% Impurity F, and not more than about 1.5% Impurity B. In one embodiment the colchicine composition comprises ultrapure colchicine comprising no more than 0.10% Impurity A, no more than about 0.15% Impurity F, and no more than 2.0% Impurity B. The pharmaceutically acceptable excipient can be one or more discussed previously herein.

In one embodiment, a colchicine composition comprises colchicine; a filler; a binder; and a disintegrant; wherein the colchicine composition comprises no more than about 3.5% total impurities. In some embodiments, the colchicine composition comprises ultrapure colchicine and total impurities in the composition comprise no more than about 3.5%, or specifically no more than about 3.0%, more specifically no more than about 2.0%, or yet more specifically, no more than about 1.0%; with individual impurity levels of not more than about 0.42% for Impurity A, Impurity C, Impurity D, Impurity E, or Impurity F, and not more than about 2.0% for Impurity B. or specifically with individual impurity levels of not more than about 0.10% for Impurity A, Impurity C, Impurity D, Impurity E, or Impurity F, and not more than about 2.0% for Impurity B.

In one embodiment, the percent total impurities in the composition is determined in an HPLC assay as described in Colchicine Official Monograph USP30/NF25 as 100% times a sum of responses of any peaks other than that due to colchicine, eluting within 1.5 times the retention time for colchicine, relative to a sum of responses of all peaks eluting within 1.5 times the retention time for colchicine and the percent of an individual impurity in the composition is determined in an HPLC assay as described in Colchicine Official Monograph USP30/NF25 as 100% times the responses of the impurity

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peak relative to a sum of responses of all peaks eluting within 1.5 times the retention time for colchicine.

In yet another embodiment, the percent total and/or individual impurities in the composition is determined in an HPLC assay or HPLC assay in accordance with the methods described in Table 2 or Table 3A or 3C.

In one embodiment, any of the colchicine compositions described above is in the form of a tablet. As used herein, the term "tablet" means a compressed pharmaceutical dosage form of any shape or size. The tablets described herein may be obtained from the compositions comprising colchicine and a pharmaceutically acceptable excipient. Any of the colchicine compositions can be in the form of any other dosage form known in the art, specifically, any oral dosage form, for example a capsule.

Either wet or dry granulation of a colchicine composition may be used prior to compressing the composition into tablets, or direct compression can be used.

In one embodiment, wet granulation is used to prepare wet granules comprising colchicine. A granulating liquid is used in wet granulation process. Both aqueous and non-aqueous liquids may be used as the granulating liquid. In one embodiment, the granulating liquid is an aqueous liquid, or more specifically, de-ionized water. In an embodiment, the colchicine is ultrapure colchicine.

The amount of the granulating liquid used may depend on many factors, for example, the type of the granulating liquid, the amount of the granulating liquid used, whether a hygroscopic excipient is used, the nature of the active agent, and the active agent loading. In one embodiment, the amount of the granulating liquid is in the range of about 5 wt % to about 50 wt %, or more specifically, about 10 wt % to about 40 wt %, based on the dry weight of the granulating particles prior to wet granulation.

Wet granulation time is generally about 5 to 60 minutes. In one embodiment, the colchicine particles and suitable excipients are mixed with the granulating liquid for a period of about 5 to about 45 minutes, or more specifically, about 5 to about 35 minutes. For a small scale, the mixing time is about 1 to about 20 minutes, or more specifically, 3 to 10 minutes. Wet granulation is generally performed at temperatures between about 20° C. to about 35° C., or more specifically, at room temperature (about 25° C.).

Any equipment may be used to contact the granulating liquid with the colchicine and the excipients as long as uniform distribution of the granulating liquid is achieved. For example, small-scale production can be achieved by mixing and wetting the ultrapure colchicine and the excipients in mortars or stainless steel bowls, while for larger quantities, V-blenders with intensifier bars, planetary mixers, rotary granulators, high shear granulators, and fluid-bed granulation equipment may be used. In one embodiment, the granulator is a high shear granulator.

In one embodiment, a method of making a colchicine composition comprises wet granulating colchicine with a pharmaceutically acceptable excipient to obtain wet granules, and mixing the granules with a second excipient to obtain a colchicine composition. In one embodiment, the pharmaceutically acceptable excipient comprises a mixture of a filler and a binder. In another embodiment, the mixture of the filler and the binder comprises pregelatinized starch, lactose monohydrate, and microcrystalline cellulose. In another embodiment, de-ionized water is used as the granulating liquid. In some embodiments, the colchicine is ultrapure colchicine. In an embodiment, the second excipient mixed with the granules is a disintegrant. The colchicine compositions can contain about

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0.1 wt % to about 10 wt %, or more specifically, about 0.1 wt % to about 1 wt %, of colchicine, based on the total weight of the colchicine composition.

In an embodiment, the method of making a composition comprises wet granulating colchicine with a pharmaceutically acceptable excipient to obtain wet granules, and mixing the granules with a disintegrant to obtain a colchicine composition. In some embodiments, the method further comprises drying the mixture. In another embodiment, the wet granules are dried to obtain dried granules; and then the dried granules are mixed with a disintegrant to obtain the composition. In another embodiment, the dried granules can be milled to obtain milled granules before mixing the milled dried granules with the disintegrant. In one embodiment, greater than 50% of the milled granules pass through a 45 micron sieve or mesh screen. The method can further comprise mixing the colchicine composition with a lubricant to obtain a tableting blend or compressing the tableting blend to obtain a tablet. The method can further comprise coating the tablet.

In one embodiment, a method of making a colchicine composition comprises wet granulating ultrapure colchicine with a pharmaceutically acceptable excipient to obtain wet granules; drying the wet granules to obtain dried granules; milling the dried granules to obtain milled granules; and mixing the milled granules with a disintegrant to obtain the composition. The ultrapure colchicine can comprise no more than about 3.0% total impurities, with no more than about 0.10% Impurity A, no more than about 0.15% Impurity F, and no more than about 2.0% Impurity B.

In another embodiment, a method of making a colchicine tablet comprises wet granulating colchicine with a pharmaceutically acceptable excipient to obtain wet granules; drying the wet granules to obtain dried granules; milling the dried granules to obtain milled granules; mixing the milled granules with a disintegrant to obtain the composition; mixing the composition with a lubricant to obtain a tableting blend; and compressing the tableting blend to obtain a colchicine tablet.

In some embodiments, the wet granules are dried to obtain dried granules before mixing with a second excipient, for example a disintegrant. Wet granules can be dried by any suitable means to remove the granulating liquid and to form dried granules containing colchicine and the pharmaceutically acceptable excipient. The conditions and duration of drying depend on factors such as the liquid used and the weight of the granulating particles. Examples of suitable drying methods include, but are not limited to, tray drying, forced air drying, microwave drying, vacuum drying and fluid bed drying.

The extent of drying may be determined by visual observation and manual manipulation, as is common in the art. The extent of drying may also be determined by sieve analysis, moisture measurements, such as loss on drying (LOD) or other suitable methods. In one embodiment, wet granules are dried until the granules lose less than 5 weight percent (wt %), or more specifically, 3 wt % upon drying at 105° C. based on the total weight of the dried granules prior to drying (or LOD of less than 3 wt %).

After drying, dried granules may be mixed directly with an excipient, for example, a filler, a binder, a disintegrant, or a lubricant, for further processing. Alternatively, dried granules may optionally be subjected to additional processing steps prior to mixing with the excipient. For example, dried granules may be sized to reduce particle size prior to mixing with an excipient. Exemplary sizing operations include milling or sieving. Any suitable equipment for reducing the particle size may be used in the present invention. In one embodiment, the

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dried granules are milled to obtain milled granules so that at least 50% of the milled granules pass through a 45 micron mesh screen.

Suitable excipients may be added extragranularly and mixed with the granules to form colchicine compositions. As used herein, the term “extragranular” or “extragranularly” means that the referenced material, for example, a suitable excipient, is added or has been added as a dry component after wet granulation. In one embodiment, a disintegrant and a lubricant, in that sequence, are added extragranularly to the granules and mixed to form a blend. The blend may be encapsulated directly into capsule shells, for example, hard gelatin shells, to form capsule formulations. Alternatively, the blend may be compressed into tablets. In some embodiments, the granules are dried granules or milled, dried granules. In some embodiments, the colchicine is ultrapure colchicine.

Mixing can be carried out for a sufficient time to produce homogeneous mixtures or blends. Mixing may be accomplished by blending, stirring, shaking, tumbling, rolling, or by any other method to achieve a homogeneous blend. In some embodiments, the components to be mixed are combined under low shear conditions in a suitable apparatus, such as a V-blender, tote blender, double cone blender or any other apparatus capable of functioning under low shear conditions. The homogenous mixtures or blends are then compressed using any method suitable in the industry.

The colchicine tablets prepared from the above described methods exhibit acceptable physical characteristics including good friability and hardness. The colchicine tablets disclosed herein have friability in the range of about 0% to 3%, specifically about 0 to 1%, more specifically 0% to 0.5%

The colchicine tablet can be coated. Coating the tablet may be performed by any known process. A coating for the colchicine tablet disclosed herein can be any suitable coating, such as, for example, a functional or a non-functional coating, or multiple functional or non-functional coatings. By “functional coating” is meant to include a coating that modifies the release properties of the total formulation, for example, a sustained-release coating. By “non-functional coating” is meant to include a coating that is not a functional coating, for example, a cosmetic coating. A non-functional coating can have some impact on the release of the active agent due to the initial dissolution, hydration, perforation of the coating, etc., but would not be considered to be a significant deviation from the non-coated composition.

In one embodiment, the tablet is coated with a non-functional coating. The coating can be a white or colored OPADRY® or OPADRY® II (both available from Colorcon, West Point, Pa.), optionally with additional ingredients such as carnauba wax, plasticizers, opacifiers, colorants, and antioxidants. In one embodiment, the coating comprises OPADRY® II and carnauba wax.

In an embodiment, a colchicine composition comprises about 0.6 mgA colchicine; about 12 to about 16 mg pregelatinized starch; about 20 to about 24 mg microcrystalline cellulose; about 3.9 to about 4.7 mg sodium starch glycolate; about 0.5 to about 0.7 mg magnesium stearate; and an amount of lactose monohydrate such that the colchicine dosage form has a total weight of about 100 mg. In some embodiments the colchicine composition comprises about 0.6 mgA colchicine, about 14 mg pregelatinized starch, about 22 mg microcrystalline cellulose, about 4.3 mg sodium starch glycolate, about 0.6 mg magnesium stearate, and an amount of lactose monohydrate such that the colchicine dosage form has a total weight of about 100 mg. The colchicine composition can be in the form of a tablet. In some embodiments the tableted

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composition further comprises a coating comprising Opadry® II and carnauba wax. In an embodiment, the colchicine is ultrapure colchicine.

In one embodiment, a colchicine composition comprising ultrapure colchicine is formulated into an immediate-release formulation. By “immediate-release” is meant a conventional or non-modified release in which greater than or equal to about 75% of the active agent is released within two hours of administration, specifically within one hour of administration.

Active agent release from a pharmaceutical formulation can be analyzed in various ways. One exemplary test is in vitro dissolution. A dissolution profile is a plot of the cumulative amount of active agent released from a formulation as a function of time. A dissolution profile can be measured utilizing the Drug Release Test <724>, which incorporates standard test USP 26 (Test <711>). A profile is characterized by the test conditions selected such as, for example, apparatus type, shaft speed, temperature, volume, and pH of the dissolution medium. More than one dissolution profile may be measured. For example, a first dissolution profile can be measured at a pH level approximating that of the stomach, and a second dissolution profile can be measured at a pH level approximating that of one point in the intestine or several pH levels approximating multiple points in the intestine.

In one embodiment, the immediate-release colchicine composition exhibits a dissolution profile such that at ten minutes after combining the composition with 500 ml of purified water at 37° C.±0.5° C. according to USP 28<711> Apparatus 1 (basket), 100 rpm speed, about 90 to about 100 wt. % of the total amount of active agent is released; specifically at 30 minutes after combining the composition with the dissolution medium, about 95 to about 100 wt. % of the total amount of colchicine is released; and more specifically at one hour after combining the composition with the dissolution medium, about 98 to about 100 wt. % of the total amount of colchicine is released.

Potency, or the amount of active colchicine present in a batch of colchicine, can be determined as described in Colchicine Official Monograph USP 30/NF 25 by comparing an assay sample to a colchicine reference standard (e.g., USP Colchicine RS) sample in the chromatographic assay described in Colchicine Official Monograph USP30/NF25. The quantity of active colchicine in the assay sample, in mg, of C<sub>22</sub>H<sub>25</sub>NO<sub>6</sub> is calculated by the formula: 10C (r<sub>t</sub>/r<sub>s</sub>), in which C is the concentration, in µg per mL, of the colchicine reference standard sample; and r<sub>t</sub> and r<sub>s</sub> are the colchicine peak responses obtained from the assay sample and the colchicine reference standard sample, respectively.

In another embodiment, potency of a batch of colchicine can be determined using the HPLC Potency assay described in the table below by comparing an assay sample to a colchicine reference standard.

HPLC Potency Assay B	
Mobile phase	50 mM Potassium Phosphate Buffer:methanl (45:55), pH 5.5 ± 0.05
Column	Phenomenex Luna C8(2), 4.6 mm × 25 cm, 5 µm
Flow rate	1.0 mL/min
Column Temperature	Ambient
Detection	254 nm
Injection volume	20 uL
Sample Conc.	0.120 mg/ml
Run time	15 min

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The quantity, in percentage, of C<sub>22</sub>H<sub>25</sub>NO<sub>6</sub> (active colchicine), on an anhydrous, solvent free basis, in the colchicine assay sample is calculated by the formula:

$$\% \text{ Purity} = \frac{r_u}{r_s} \times \frac{W_s(\text{mg}) \times P \times \left( \frac{100 - M_s - S_s}{100} \right)}{500 \text{ ml}} \times \frac{PV(\text{ml})}{VF(\text{ml})} \times \frac{VF_1(\text{ml})}{SW(\text{mg}) \times \left( \frac{100 - M_u - S_u}{100} \right)} \times \frac{VF_2(\text{ml})}{PV_1(\text{ml})} \times 100$$

Where:

- r<sub>u</sub>=The peak area of colchicine in the working sample solution
- r<sub>s</sub>=The peak area of colchicine in the working standard solution
- W<sub>s</sub>=The weight of colchicine in the standard preparation
- P=Standard purity factor expressed as labeled % Purity
- M<sub>s</sub>=Moisture factor in standard expressed as % Moisture
- S<sub>s</sub>=Solvent factor in standard expressed as % Solvent
- PV=Pipet volume used for the working standard solution
- VF=Volumetric flask used for the working standard solution
- SW=Sample weight in the stock sample solution
- VF<sub>1</sub>=Volumetric flask used for the stock sample solution
- M<sub>u</sub>=Moisture factor in sample expressed as % Moisture
- S<sub>u</sub>=Solvent factor in sample expressed as % Solvent
- VF<sub>2</sub>=Volumetric flask used for the working sample solution
- PV<sub>1</sub>=Pipet volume used for the working sample solution.

Alternatively, potency of a batch of colchicine can be determined by comparing an assay sample to a colchicine reference standard in yet another HPLC assay as follows:

HPLC Potency Assay C	
HPLC System:	HPLC equipped with a pump, autosampler, variable wavelength detector and a suitable data acquisition system
Column Information:	Phenomenex Gemini C18 150 × 4.6 mm 5 µm 110 Å
Detection:	245 nm
Flow Rate:	1.5 mL/minute
Injection Volume:	20 µL
Column Temperature:	30° C. ± 3° C.
Needle Rinse Setting:	Double
Sampling Rate:	2.0
Resolution:	1.2
Filter Response:	1.0
Digital Filter:	Enabled
Needle Wash/Seal Wash:	Methanol:Water (50:50)
Run Time:	About 15 minutes
Mobile Phase:	pH 6.0 Buffer Solution (50 mM of Potassium phosphate and 4 mM of EDTA):Methanol (60:40)
Diluent:	Water:Methanol (75:25)

The percent purity of Colchicine (C<sub>22</sub>H<sub>25</sub>NO<sub>6</sub>), on an anhydrous, solvent-free basis, is calculated as follows:

$$\% \text{ Assay} = \frac{r_u}{r_s} \times \frac{W_s(\text{mg}) \times P}{50 \text{ mL}} \times \left( \frac{100 - \% RS_s - \% W_s}{100} \right) \times$$

-continued

$$\frac{5.0 \text{ mL}}{100 \text{ mL}} \times \frac{500 \text{ mL}}{W_u(\text{mg}) \times \left( \frac{100 - \% RS_u - \% W_u}{100} \right)} \times 100\%$$

Where:

r<sub>u</sub>=The peak area response of Colchicine in the Sample Solution.

r<sub>s</sub>=The peak area response of Colchicine in the Working Standard Solution.

W<sub>s</sub>=The weight of Colchicine in the Stock Standard Preparation.

W<sub>u</sub>=The weight of Colchicine in the Sample Preparation.

P=Standard purity factor expressed as labeled (% Purity/100).

% RS<sub>s/u</sub>=Percent of Residual Solvents in the Colchicine Standard/Sample.

% W<sub>s/u</sub>=% Water in the Colchicine Standard/Sample.

Disclosed herein are also methods of treatment and dosing regimens.

The compositions comprising ultrapure colchicine disclosed herein may be used to treat or prevent a patient's condition such as acute gouty arthritis, chronic gouty arthritis, acute pericarditis, asthma, Behçet's disease, cancer, chronic gout (prophylaxis), pseudogout cystic disease comprising polycystic kidney disease or cystic fibrosis, demyelinating disease of central or peripheral origin, Dupuytren's contracture, Familial Mediterranean fever, glaucoma, idiopathic pulmonary fibrosis, idiopathic thrombocytopenic purpura, inflammatory disorder comprising rheumatoid arthritis, lentiviral infection, multiple sclerosis, postpericardiotomy syndrome, primary amyloidosis, primary biliary cirrhosis, proliferative vitreoretinopathy, pyoderma gangrenosum, recurrent pericarditis, or a condition in need of enhanced bone formation or bone mineral density.

The traditional dose of colchicine used to treat or prevent an attack of acute gouty arthritis has been about 1.0 to about 1.2 mgA of colchicine, for example, two tablets each comprising about 0.6 mgA colchicine. This dose may be followed by one unit of the composition every hour, or two units every two hours, until pain is relieved or until diarrhea ensues ("diarrheal dose"). After the initial dose, it is sometimes sufficient to take about 0.6 mgA colchicine every two or three hours. The dosing should be stopped if there is gastrointestinal discomfort or diarrhea. (Opiates may be needed to control diarrhea.) In subsequent attacks, the patient should be able to judge his medication requirement accurately enough to stop short of his diarrheal dose. The total amount of colchicine needed to control pain and inflammation during an attack has been believed to be in the range from about 4 mgA to about 8 mgA. An interval of three days between colchicine courses is advised in order to minimize the possibility of cumulative toxicity.

In one embodiment, a method of treating acute gouty arthritis comprises administering two colchicine dosage forms each comprising about 0.6 mgA colchicine at the onset of the acute gout attack, followed by one dosage form every hour for m hours, wherein the value of m is 1 to 8. In one embodiment, the value of m is 1 to 6. In another embodiment, the value of m is 1 (total of 3 tablets). In yet another embodiment, the value of m is 6 (total of 8 tablets). The colchicine in the dosage form can be ultrapure colchicine. The dosage form can be any oral dosage form, specifically a tablet.

In another embodiment, a method of treating Familial Mediterranean Fever comprises administering 1/2 dosage form to four dosage forms daily, each dosage form comprising

ing about 0.6 mgA colchicine (total of about 0.3 to about 2.4 mgA colchicine daily). In another embodiment, a method of prophylactically treating chronic gout comprises administering one-half dosage form, one dosage form, two dosage forms, or three dosage forms, each dosage form comprising about 0.6 mgA of colchicine, daily. In another embodiment, a method of treating Behçet's disease comprises administering one dosage form comprising about 0.6 mgA of colchicine twice daily (total of 2 dosage forms). The colchicine in the dosage form can be ultrapure colchicine. The dosage form can be any oral dosage form, specifically a tablet.

In one embodiment, a method of treating patients with some but not all of the symptoms of acute gout, chronic gout (prophylaxis), or pseudogout, where the patients are not clinically or informally diagnosed with one of these diseases, comprises administering one or more of the dosage forms comprising about 0.6 mgA of colchicine. The colchicine in the dosage form can be ultrapure colchicine.

The invention should not be considered limited to these particular conditions for combining the components and it will be understood, based on this disclosure that the advantageous properties can be achieved through other conditions provided the components retain their basic properties and substantial homogeneity of the blended formulation components of the formulation is otherwise achieved without any significant segregation.

The following examples further illustrate the invention but should not be construed as in any way limiting its scope. In particular, the processing conditions are merely exemplary and can be readily varied by one of ordinary skill in the art.

EXAMPLES

Example 1

Exemplary Ultrapure Colchicine

As discussed above, ultrapure colchicine with reduced levels of individual and total impurities was desired by the inventors for formulation into a new dosage form in order to minimize potential adverse reactions from the impurities in patients taking the dosage form and to reduce the expense of qualification testing during the approval process for marketing the new dosage form. Batches of conventional colchicine were previously obtained from Sanmar Specialty Chemicals Limited (Berigari, India). Conventional colchicine can be further purified to form ultrapure colchicine meeting the following impurity specifications:

TABLE 4

Purity Specifications for an exemplary batch of Ultrapure Colchicine		
Impurity, Common name	Impurity	NMT %
N-deacetyl-N-formyl colchicine	A	0.10
Conformational isomer	B	1.0
β-Lumicolchicine	C	0.10
Colchicoside	D	0.10
3-O-demethyl colchicine	E	0.10
Total Impurities		2.0

Ultrapure colchicine was prepared to meet the purity specifications in Table 4 as described below.

First, conventional colchicine was obtained from a colchicine chloroform extract. The extract was washed with a mixture of purified water, sodium hydroxide solution, sodium chloride solution and acetic acid. The washed extract was

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filtered and the resulting concentrate was distilled in two steps, first using methanol, and second using ethyl acetate. The resulting distillate was crystallized. Ethyl acetate was used to isolate and wash the crystallized colchicine, which was then dried, resulting in the conventional colchicine. This process is also referred to herein as the “old process”.

Second, the conventional colchicine was then subjected to column chromatography on neutral alumina using methylene chloride as solvent. The resulting concentrate was distilled using ethyl acetate, crystallized, isolated and washed using ethyl acetate, and dried, resulting in ultrapure colchicine. This method of generating conventional colchicine, followed by the additional chromatography purification step is also referred to herein as the “new process”.

The impurity levels of the lot of ultrapure colchicine and two lots of conventional colchicine were analyzed using the USP30/NF25 Colchicine Official Monograph HPLC method (“USP method”) described in Table 2 above. The impurity levels are shown in Table 5.

TABLE 5

Colchicine Lot	Impurity Level, %			
	N-Deacetyl-N-formyl colchicine - Impurity A	Conformational Isomer - Impurity B	Total Unidentified Impurities	Total Impurities
Ultrapure (RD0600164)	ND*	0.5	ND*	0.5
Conventional-1 (RD060075)	2.1	0.6	ND*	2.7
Conventional 2 (RD060055)	2.2	0.6	ND*	2.8

\*ND—None detected.

Table 5 shows that ultrapure colchicine has fewer impurities than each of the conventional colchicine lots. Total impurities of the Ultrapure Lot using the USP method were about 0.5%. On the other hand, total impurities of conventional Lots #1 and 2 were about 2.7% and 2.6%, respectively.

Determined impurity levels may differ depending on the test method used. Table 5B contrasts the determined levels of the conformational isomer, Impurity A (N-deacetyl-N-formyl colchicine), and total impurities for the three colchicine lots using the three methods described in Table 2. The three methods show a maximum absolute variability in the percent determined of 0.8% for N-deacetyl-N-formyl colchicine, of 0.5% for conformational isomer, and 0.7% for total impurities.

TABLE 5B

Levels of impurities in colchicine lots determined using methods of Table 2.										
Lot name (Lot #)	Purification Process	Conformational Isomer			N-deacetyl-N-formyl colchicine			Total Impurities		
		UPLC Method	HPLC Method	USP Method	UPLC Method	HPLC Method	USP Method	UPLC Method	HPLC Method	USP Method
Conventional-1 (RD060055)	Old	0.9	0.8	0.6	3.0	2.5	2.2		3.5	2.8
Conventional 2 (RD060075)	Old	0.9	0.8	0.6	2.7	2.3	2.1		3.2	2.7
Ultrapure (RD0600164)	New	0.9	1.0	0.5	ND*	ND	ND		1.1	0.5

\*ND, none detected.

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Regardless of the testing method used for measuring these impurity levels, the impurity levels for ultrapure colchicine manufactured using the new process remains below the specifications set forth in Table 4.

The ultrapure colchicine of the present invention was prepared to meet the organic volatile impurity specifications (“residual solvents”) in Table 6 as described below. The residual solvents are determined using USP <467> test method. In addition to the known and existing solvents, specifications were also set for residual solvent peaks that were seen in HPLC assay testing as described in Tables 2, 3A, or 3C, which solvents are not expected or previously existing for the residual solvent test methods for colchicine or were not identifiable.

TABLE 6

Specifications for Organic Volatile Impurities	
Organic volatile	NMT
Chloroform	100 ppm
Methanol	3000 ppm
Methylene Chloride	600 ppm
Ethanol	5000 ppm
Ethyl Acetate	6.0%
Ethyl Propionate	5000 ppm
Propyl Acetate	5000 ppm
Others	500 ppm each

## Example 2

## Stable Tablets Comprising Ultrapure Colchicine

Stable colchicine compositions comprising the ultrapure colchicine described in Example 1 were manufactured using the following process. Ultrapure colchicine as described in Example 1 was dissolved in purified water. Pregelatinized starch (Starch® 1500), lactose monohydrate, NF (Fast Flo), and microcrystalline cellulose, NF (Avicel PH101) were placed in a 150-liter high shear granulator and mixed. The aqueous ultrapure colchicine solution was added to the granulator while mixing. The wet granules were dried in an oven at 50° C. until the loss on drying of the material was less than 3 wt %. The dried granules were milled through a Fitzmill equipped with a 1A screen.

The milled granules were charged into a 5 cubic foot Gemco Double Cone Blender and blended with screened sodium starch glycolate, NF (GLYCOLYS®). Then,

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screened magnesium stearate, NF was added to the blender. Blending was continued and a final tableting blend was made. This final tableting blend was compressed into core tablets. These core tablets were film-coated with OPADRY®II purple and carnauba wax. The composition of the ultrapure colchicine tablets is shown in Table 7.

TABLE 7

Ingredient	Amount Per Tablet, mg
Ultrapure Colchicine	0.6 <sup>1</sup>
Pregelatinized starch, NF (Starch 1500)	14.0
Lactose Monohydrate, NF (Fast Flo)	Varies <sup>2</sup>
Microcrystalline Cellulose, NF (Avicel PH101)	21.6
Sodium Starch Glycolate, NF (GLYCOLYS)	4.3
Magnesium Stearate, NF	0.6
Total core tablet	100

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TABLE 7-continued

Ingredient	Amount Per Tablet, mg
OPADRY II Purple (#40L10039)	4.0
Carnauba Wax	0.01

<sup>1</sup>Colchicine amount is shown in units of mgA, adjusted for purity of the lot of colchicine.

<sup>2</sup>Amount adjusted, depending on the actual amount of the colchicine lot added, to maintain an overall core tablet weight of 100 mg.

As a comparison, the lot of conventional colchicine designated in Example 1 as “conventional-2” was substituted in place of ultrapure colchicine in the same tablet formulation shown in Table 7. The same process of making the tablets as described above was used.

The impurities in the tablet comprising the ultrapure colchicine and that comprising the conventional colchicine were analyzed using the HPLC method described in Table 2 above. The impurity levels of both colchicine tablets are shown in Table 8.

TABLE 8

		Impurity Content, %				
Colchicine Product Lot	Colchicine Lot	Process	N-Deacetyl-N-formyl colchicine (Impurity A)	Conformation Isomer (Impurity B)	Total Unknown Impurities	Total Impurities
A	Ultrapure	New	ND*	1.1	0.1	1.2
B	Conventional-2	Old	2.3	1.2	ND*	3.6

\*ND—None detected.

It can be seen from Table 8 that the tablet comprising the ultrapure colchicine has less total impurities than that comprising the conventional colchicine.

The colchicine composition comprising ultrapure colchicine at 6 month stability time points under conditions of 25° C./60% relative humidity and 40° C./60% relative humidity exhibits impurity content ranges of Not Detected to about 0.1% for Impurity A, less than about 1.0% for total unknown impurities compared to a colchicine composition comprising conventional colchicine which exhibits impurity content of greater than about 1.5 for Impurity A and greater than about 2.0% for total unknown impurities when tested under the same conditions.

Table 9 below provides data on impurity levels and stability of impurity levels of colchicine composition batches manufactured using ultrapure and conventional colchicine, and impurity levels for two lots of commercially available COL-PROBENECID® tablets (Watson Laboratories), an FDA-approved combination dosage form comprising colchicine and probenecid.

TABLE 9

Material	Lot	Colchicine		Conformational Isomer		N-Deacetyl peak	
		purification Process	Conditions of Stability Study	UPLC Method	HPLC Method	UPLC Method	HPLC Method
COL-PROBENECID® (Probenecid/Colchicine) Tablets†	L6C0395	N/A	N/A	0.8	—	2.2	—
	L6M1440	N/A	N/A	0.8	—	2.5	—
Colchicine Product Lot	B	Old process	room temp, at release	0.9	1.2	2.8	2.3
			12 mo 25 C./60% RH	0.9	0.9	2.7	2.6
	A	New process	room temp, at release	1.0	1.2	ND	ND
			6 mo 25 C./60% RH	1.0	0.8	ND	ND
			6 mo 40 C./75% RH	1.0	1.1	ND	ND
			6 mo 25 C./60% RH	1.0	1.1	ND	ND
	C	New process	6 mo 25 C./60% RH	0.9	0.9	ND	ND
			6 mo 40 C./75% RH	1.0	1.1	ND	ND

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TABLE 9-continued

Material	Lot	Colchicine		Conformational Isomer		N-Deacetyl peak	
		purification Process	Conditions of Stability Study	UPLC Method	HPLC Method	UPLC Method	HPLC Method
	D	New process	room temp, at release 6 mo 25 C./60% RH 6 mo 40 C./75% RH	1.0 1.0 0.9	1.1 1.0 1.1	ND ND ND	ND ND ND

—, not analyzed;

†Commercially available;

N/A, not applicable;

ND, none detected.

For comparison, several lots of an FDA-approved colchicine-probenecid combination dosage form and various unapproved commercial colchicine dosage forms were tested for levels of impurities using the HPLC method of Table 2. Results are shown in the tables below.

Impurities in FDA-Approved Colchicine/Probenecid Combination Product				
Watson Laboratories Colchicine/Probenecid Tablets				
Impurity	L7G1085	L7G1085	L7G1087	L7E0808
Conformational Isomer	1.0%	1.0%	0.8%	1.0%
N-deacetyl-N-formyl colchicine	2.0%	2.0%	1.5%	2.0%
Largest Unknown	0.1%	0.1%	0.1%	0.1%
Total Impurities	3.1%	3.1%	2.4%	3.2%

Summary of Impurities in Marketed Colchicine Products with Batches of colchicine tablets using ultrapure colchicine			
Impurity	Marketed Colchicine Products		Product Lots with Ultrapure Colchicine
	Minimum	Maximum	Maximum
Conformational Isomer	0.8%	1.1%	1.1%
N-deacetyl-N-formyl colchicine	1.3%	2.7%	ND
Largest Unknown	0.1%	1.7%	0.3%
Total Impurities	2.4%	5.3%	1.4%

ND = none detected

The total impurities found in ultrapure colchicine and colchicine products comprising ultrapure colchicine are significantly lower compared to the approved and unapproved, marketed colchicine products. In addition, the maximum total impurities value observed by testing 14 approved or unapproved marketed products was 5.3%; while the maximum

Impurities in Unapproved Colchicine Products						
Impurity	West-Ward			Vision		
	62303A*	63842A	63843A	C07003	C07049	C07058
Exp Date	January-2009	May-2011	May-2011	January-2009	August-2009	September-2009
Conformational Isomer	1.1/0.9%	0.9%	0.9%	1.1/0.8%	0.9%	0.9%
N-deacetyl-N-formyl colchicine	2.5/2.6%	2.0%	1.8%	1.3/1.3%	2.7%	2.6%
Largest Unknown	1.7/1.6%	0.5%	0.3%	0.1/0.1%	0.1%	0.3%
Total Impurities	5.3/5.3%	3.5%	3.1%	2.5/2.3%	3.8%	4.0%

Impurity	Qualitest			Akyma
	T105G07A	T107G07A	T108G07A	3A5246004*
Exp Date	July-2010	July-2010	August-2010	January-2008
Conformational Isomer	1.0%	0.9%	0.9%	1.1/0.9%
N-deacetyl-N-formyl colchicine	%1.4	1.3%	1.3%	1.4/1.5%
Largest Unknown	0.3%	0.2%	0.2%	0.2/0.1%
Total Impurities	2.7%	2.7%	2.6%	2.9/2.5%

\*Values from two separate analyses reported

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value seen to date in inventive ultrapure colchicine product batches was 1.4%. This represents a 75% reduction in total impurities.

Of particular significance, the level of the known impurity, N-deacetyl-N-formyl-colchicine (Impurity A, also known as Gloriosine) has been reduced from levels exceeding 2% to levels to undetectable levels that comply with the ICH Q3A (R2) qualification threshold of 0.15% for an active agent. Gloriosine is tumorigenic and has been studied as an anti-cancer agent. Purification of conventional colchicine to obtain ultrapure colchicine has effectively reduced all individual impurity levels in the colchicine to substantially reduce exposure of patients to this tumorigenic impurity.

### Example 3

#### Therapeutic Effects of Ultrapure Colchicine Formulation

The therapeutic effect of the ultrapure colchicine formulation containing 0.6 mgA of colchicine obtained in Example 2 is evaluated in a clinical study that is a multicenter, randomized, double-blind, placebo-controlled, parallel group, 1-week, dose comparison study designed to evaluate the efficacy of ultrapure colchicine in treating an acute gout attack (acute gouty arthritic attack) in patients with acute gout. A sufficient number of patients are screened to enroll and randomize 300 patients (100 patients per treatment group) who meet the criteria of the American College of Rheumatology (ACR) for acute arthritis of gout. The primary objective of the study is to demonstrate the efficacy of colchicine in an acute gout attack (gouty flare) based on pain reduction after 24 hours as a measure of response. Secondary objectives of the study are to compare low-dose and standard-dose dosing regimens of colchicine with respect to pain, time to response and complete pain relief, interference with sleep, and signs and symptoms of inflammation and to determine the safety of colchicine when administered in the two different dosing regimens.

#### Description of Study

The study will consist of three distinct phases and the number of visits to the study clinic will vary depending on conditions pertaining to an individual patient's acute gout flare experienced in the study as described below. The Pre-Flare Phase will consist of up to two visits to the study clinic (with additional interim visits for clinical laboratory testing every 3 months until acute gout flare onset): Visit 1 (Screening) and Visit 2 (Randomization). The Flare Phase will not include a visit to the study clinic. The Post-Flare Phase will consist of up to three visits to the study clinic: Visit 3 (as soon as possible [ASAP] up to 48 hours post-flare onset; if a patient cannot complete Visit 3 in the first 48 hours post-flare onset, Visit 3 will be waived and the patient should return to the clinic for Visit 4), Visit 4 (>48 to 96 hours post-flare onset in patients who took at least one dose of study drug and in patients who did not qualify for treatment with study drug during the Flare Phase but did not complete Visit 3), and Visit 5 (7 days post-flare onset to be conducted in patients who took at least one dose of study drug and whose acute gout flare was still ongoing at Visit 4). For those patients in whom the acute gout flare is not resolved at Visit 5 (based on the judgment of the Investigator) or in whom there is an unresolved AE or clinically significant treatment-emergent laboratory abnormality, there will be one additional follow-up visit 14 days post-flare onset (Visit 6).

When a patient develops an acute gout flare, the patient will call the trained personnel at the Gout Flare Call Center (avail-

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able 24 hours/day throughout the duration of the study). The patient will be queried regarding any changes in his/her medical health and concomitant medication use since the time of randomization. In order to establish if the patient's acute gout flare will be eligible for treatment with study drug, a standardized questionnaire will be used to document that the patient has all of the following signs/symptoms of the affected joint(s): swelling, erythema, marked tenderness, and pain. In addition, a patient must have at least one of the following: rapid onset of maximum pain within the prior 4 to 12 hours, decreased range of motion in the joint, warmth, or other symptom similar to a prior gout flare. Patients will be asked to rate the pain severity for each joint affected by the acute gout flare by using a study diary. Patients must have at least one joint affected by an acute gout flare with a pain assessment of  $\geq 4$  on the PI-NRS at the onset of the acute gout flare during the Flare Phase prior to taking study drug. If signs and symptoms of an acute gout flare are confirmed and the gout flare is considered eligible for treatment with study drug, the patient will also be instructed to begin taking study drug and to continue completing the patient diary. Patients will be instructed to stop taking study drug and to call the investigational site if at any time they experience a severe gastrointestinal event while taking study drug. The Gout Flare Call Center will call the patient in 24 hours from the onset of the acute gout flare to ensure that the patient has completed the patient diary, including assessments for pain at 24 hours.

In the event that the Gout Flare Call Center determines that the patient does not qualify for treatment with study drug, the patient may be asked to call back in 1 hour for re-assessment. Patients who do not qualify for treatment with study drug may seek alternative therapy without prejudice to further study participation should another acute gout flare occur.

The Gout Flare Call Center will contact patients on a monthly basis beginning 1 month after randomization to study drug. These contacts will continue until the patient has an acute gout flare or study completion, whichever occurs first. The purpose of these contacts is to re-educate patients about study participation.

#### Post-Flare Phase:

Visit 3: After developing an acute gout flare, whether eligible for treatment with study drug or not, all patients will return to the clinic as soon as possible after acute gout flare onset for clinical assessments. If a patient cannot complete Visit 3 in the first 48 hours post-flare onset, Visit 3 will be waived and the patient should return to the clinic for Visit 4. For patients whose acute gout flare was deemed eligible for treatment with study drug and at least one dose of study drug was taken, Investigators will examine the patient and complete clinical assessments, patient diaries will be collected, the patient will be queried for concomitant medication use and Adverse Events (AEs), and the study drug blister pack will be collected. For patients whose acute gout flare was deemed not eligible for treatment with study drug by the Gout Flare Call Center, continued eligibility for the study will be confirmed by the Investigator based on review of the inclusion and exclusion criteria as well as the responses to the standardized questionnaire and examination of the patient. Patient diaries will be collected and patients will be queried for concomitant medication use and AEs.

Visit 4: The second Post-Flare Phase visit is to be conducted >48 to 96 hours following acute gout flare onset. It will take place in patients who took at least one dose of study drug and also in those patients who did not qualify for treatment with study drug during the Flare Phase but did not complete Visit 3. For patients whose acute gout flare was deemed eligible for treatment with study drug and at least one dose of

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study drug was taken, Investigators will examine the patient and complete clinical assessments, patient diaries will be collected, patients will be queried for concomitant medication use and AEs, and the study drug blister pack will be collected (if not previously collected). Patients who took at least one dose of study drug and whose acute gout flare is still ongoing at Visit 4 will return to the clinic for a final visit (Visit 5) 7 days post-flare onset; however, if their acute gout flare is resolved at Visit 4, final study assessments, including collection of samples for laboratory safety and a complete physical examination, will be performed at Visit 4. For patients whose acute gout flare was deemed not eligible for treatment with study drug by the Gout Flare Call Center who did not have a Visit 3, continued eligibility for the study will be confirmed by the Investigator based on review of the inclusion and exclusion criteria as well as the responses to the standardized questionnaire and examination of the patient. Patient diaries will be collected and patients will be queried for concomitant medication use and AEs.

Visit 5/Early Termination: The final visit for the study will take place 7 days after the acute gout flare onset in patients who took at least one dose of study drug and whose acute gout flare was still ongoing at Visit 4. Patients will be examined and clinical assessments will be made. A complete physical examination will be conducted. Samples for clinical laboratory testing will be collected. Patient diaries will be collected and patients will be queried for concomitant medication use and AEs. The study drug blister pack will be collected (if not previously collected).

Visit 6/Follow-up: For those patients in whom the acute gout flare is not resolved at Visit 5 (based on the judgment of the Investigator) or in whom there is an unresolved AE or clinically significant treatment-emergent laboratory abnormality, there will be one additional follow-up visit 14 days post-flare onset (Visit 6).

For inclusion in the study, a patient must be 18 years of age or older, must present with a confirmed diagnosis of gout consistent with the criteria of the ACR, and must have experienced  $\geq 2$  acute gouty arthritic attacks in the 12 months prior to randomization. Patients on urate-lowering therapy must be on a stable dose and schedule with no changes in therapy for 4 weeks prior to randomization and expected to remain on a stable regimen during study participation.

Patients with acute polyarticular gout ( $>4$  joints); taking colchicine routinely; with a known hypersensitivity to colchicine; with a history of myocardial infarction, unstable angina, cerebrovascular events, or coronary artery bypass grafting; with active myeloid leukemia, obstructive gastrointestinal cancer, or metastatic cancer; with chronic renal dysfunction, with chronic hepatic dysfunction are excluded from the study. Patients using systemic corticosteroid, cyclosporine, adalimumab, etanercept, infliximab, anakinra, abatacept, mycophenolate, azathioprine, or chronic use of non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, tramadol, and other analgesics such as opiates at screening are also be excluded.

The three treatment groups in this study are two ultrapure colchicine tablets (1.2 mgA) administered at the onset of an acute gout attack followed by one tablet (0.6 mgA) after one hour and one placebo tablet every hour thereafter for 5 hours (the "low" dose regimen); two ultrapure colchicine tablets (1.2 mgA) administered at the onset of an acute gout attack followed by one tablet (0.6 mgA) every hour for six (6) hours (the "standard" dose regimen); or two placebo tablets at the onset of an acute gout attack followed by one placebo capsule every hour thereafter for 6 hours (the "placebo" regimen).

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Efficacy assessment will be made based on patient and Investigator inputs. Patients will record pain severity and sleep interference on a study diary. The severity of pain for each joint affected by the acute gouty arthritic attack will be rated on an 11-point pain intensity numerical rating scale (PI-NRS) that ranges from 0 ("no pain") to 10 ("worst possible pain"). Recordings are to be made prior to each dose of study drug, i.e., pre-treatment with study drug and for the first 8 hours following start of treatment, and every 8 hours thereafter (while awake) until symptoms disappear or 72 hours have passed since the first dose of study drug was taken, whichever occurs first. The patient's pain assessment of each affected joint as reported by the patient at pre-treatment with study drug and at 24 hours post-start of study drug will be documented by a central Study Center to be used in the event the patient fails to provide data on his/her study diary for either of these two key time points. In the morning upon awakening, the patient is to rate sleep interference due to the acute gout flare in the study diary on an 11-point scale that ranges from 0 ("pain did not interfere with sleep") to 10 ("pain completely interfered; patient was unable to sleep"). Investigators will provide clinical assessments in the clinic at all Post-Flare Phase study visits, and at medically necessary intervening visits. For these assessments, each of the patient's joints affected by the acute gouty arthritic attack will be examined and signs and symptoms of inflammation will be rated (erythema [absent, present, or not assessable], swelling [0, "none" to 3, "severe"], and tenderness to touch [0, "none" to 3, "severe"]). At the final clinic visit, the Investigator will also provide a global assessment of response to treatment ranging from 0 ("excellent") to 4 ("none").

The primary efficacy variable is response to treatment in the target joint, based on patient self-assessment of pain at 24 hours post-dose. The target joint is identified during data analysis as that joint affected by the acute gout flare with the highest baseline pain score on the patient diary. Ties among maximum joint scores for an individual are resolved by random selection. A responder is one who provides both a pre-treatment and valid 24-hour pain score and achieves a  $\geq 50\%$  reduction in pain score at the 24-hour post-dose assessment relative to the pre-treatment score and does not use rescue medication. Patients who use rescue medication, discontinue prior to the 24-hour post-dose assessment, or do not achieve a  $\geq 50\%$  reduction in pain score at the 24 hour post-dose assessment relative to the pre-treatment score are deemed non-responders.

The secondary efficacy variables are assessments of magnitude of pain reduction, time to response, time to complete pain relief, and interference with sleep as recorded on patient diaries by the patient. Signs and symptoms of inflammation per Investigator's clinical assessments of the target joint are evaluated. Time to drop out (use of rescue medications) is also evaluated. Investigator global assessment of response to treatment is assessed.

The primary efficacy analysis will be based on an Intent-to-Treat (ITT) population, defined as all patients who were randomized, contacted the Gout Flare Call Center, took at least one dose of study drug, and had one subsequent contact. The Per Protocol (PP) population is defined as the subset of the ITT population confirmed by the Investigator as continuing to meet all major inclusion and exclusion criteria and initiating treatment within 12 hours of the onset of the acute gout flare. Analyses will also be made on an Evaluable patient population with an Evaluable patient defined as one who, in addition to being included in the PP population, completed the randomized treatment course. The ITT population will be used for the evaluation of safety.

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Statistical tests for efficacy analysis are two-tailed with an alpha significance level of 0.05.

For primary efficacy analysis, the number of responders in the standard-dose colchicine group and the placebo group, as defined for the primary efficacy variable, will be compared using the Mantel-Haenszel chi-square test stratified on study site. The comparison of the standard-dose colchicine and placebo groups of the ITT population is the primary comparison of interest. The sensitivity to alternate definitions of response (based both on magnitude of reduction from baseline as well as time point) will be evaluated as secondary endpoints. As additional sensitivity analyses, these tests will also be repeated for the PP and Evaluable populations if the sample sizes differ from the overall ITT population by more than 10%.

For secondary efficacy analysis, the number of responders in the low-dose colchicine group will be compared to placebo and also to standard-dose colchicine using the Mantel-Haenszel chi-square test stratified on study site. Change in pain intensity, interference with sleep, time to 50% reduction in pain, and time to complete pain relief will be analyzed as continuous variables using analysis of covariance with study site, treatment group, and site by treatment interaction as independent variables for change in pain intensity and interference with sleep, with baseline score as a covariate. For the Investigator's clinical assessment of inflammation (erythema, swelling, and tenderness to touch) and Investiga-

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will be conducted at the final clinic visit (Visit 4 or Visit 5). Vital signs and body weight will be measured at each Post Flare visit (Visit 3 and 4 or 5). For those patients in whom there is an unresolved AE or clinically significant treatment emergent laboratory abnormality, there will be one additional follow up visit 14 days post flare onset (Visit 6).

Safety analysis will be performed by coding adverse events using a standardized medical dictionary and the incidence summarized by treatment group; tabulations will be prepared of all AEs as well as by relationship and by severity. Adverse events resulting in termination and events meeting regulatory criteria for seriousness will also be tabulated separately. Descriptive statistics (mean, median, standard deviation, and range) of clinical laboratory testing results and vital sign measurements will be generated for each treatment group and change from the most recent value prior to onset of the acute gout flare calculated; no inferential testing will be performed. Treatment emergent abnormalities on physical examination will be tabulated and listed by treatment group. By patient listings of all safety data and concomitant medication use will be generated.

## Study Results

The following data were obtained in general accordance with the above protocol.

Out of 813 patients screened, 575 were randomized to treatment with 185 patients having a gouty flare and receiving study drug. The intent-to-treat population consisted of 184 patients (52 received standard dose, 74 received low dose and 58 received placebo).

Number of Responders Based on Target Joint Pain Score at 24 Hours Post First Dose					
Colchicine Dose		Placebo	Odds Ratio (95% Confidence Intervals)		
Low (N = 74) N (%)	High (N = 52) N (%)	(N = 58) N (%)	Low vs. Placebo	High vs. Placebo	High vs. Low
28 (37.8)	17 (32.7)	9 (15.5)	3.31 (1.41, 7.77) P = 0.0046	2.64 (1.06, 6.62) P = 0.0343	0.80 (0.38, 1.68) P = 0.5529

tor's global assessment of response to treatment, the treatment groups will be compared using the Mantel-Haenszel chi-square test stratified on study site.

Safety assessments will be made based on patient and Investigator inputs. Patients will be initially screened in the clinic for inclusion by review of medical history and concomitant medication use, physical examination, measurement of vital signs (oral temperature, sitting radial or brachial pulse rate, respiratory rate, and sitting blood pressure), body weight, and clinical laboratory testing (serum biochemistry, complete blood count, and urinalysis). After randomization, clinical laboratory tests, concomitant medication use, medical history and current complaints (AE) will be reviewed every 3 months until an acute gout flare occurs in order to ensure continued eligibility. Compliance with key inclusion/exclusion criteria (based on intervening medical history and concomitant medication use) will be reconfirmed by the Gout Flare Call Center prior to authorizing the start of study drug. Following the start of study drug, patients will record any severe gastrointestinal AEs on their diaries and these will be recorded in the Case Report Form (CRF) at each clinic visit. Full physical examinations and clinical laboratory testing

Cumulative Distribution of Degree of Percent Improvement for Target Joint Pain Score at 24 Hours Post First Dose				
Colchicine Dose				
% Improvement	High (N = 52)	Low (N = 74)	Placebo (N = 58)	
>=0%	52 (100.0%)	74 (100.0%)	58 (100.0%)	
>=10%	32 (61.5%)	47 (63.5%)	24 (41.4%)	
>=20%	29 (55.8%)	45 (60.8%)	21 (36.2%)	
>=30%	21 (40.4%)	39 (52.7%)	17 (29.3%)	
>=40%	21 (40.4%)	36 (48.6%)	14 (24.1%)	
>=50%	19 (36.5%)	30 (40.5%)	10 (17.2%)	
>=60%	15 (28.8%)	24 (32.4%)	7 (12.1%)	
>=70%	10 (19.2%)	20 (27.0%)	4 (6.9%)	
>=80%	9 (17.3%)	15 (20.3%)	3 (5.2%)	
>=90%	6 (11.5%)	9 (12.2%)	2 (3.4%)	
>=100%	6 (11.5%)	8 (10.8%)	2 (3.4%)	

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Treatment Response Based on at Least a 2-Unit Reduction in Target Joint Pain Score at 24 Hours and 32 Hours Post First Dose						
Hours Post First Dose	Number (%) of Responders			Treatment Comparisons		
	Colchicine Dose			(Odds Ratio and 95% CI) <sup>1</sup>		
	High (N = 52)	Low (N = 74)	Placebo (N = 58)	High vs. Placebo	Low vs. Placebo	High vs. Low
24	18 (34.6)	32 (43.2)	10 (17.2)	2.54 (1.04, 6.18) p = 0.0368	3.66 (1.61, 8.32) p = 0.0015	0.69 (0.33, 1.45) p = 0.3298
32	20 (38.5)	34 (45.9)	10 (17.2)	3.00 (1.24, 7.24) p = 0.0126	4.08 (1.80, 9.27) p = 0.0005	0.74 (0.36, 1.51) p = 0.4033

<sup>1</sup>The p-value is from the unstratified Pearson chi-square test.

Target Joint Pain at Baseline, 24 Hours and 32 Hours Post First Dose, and Change from Baseline (LOCF) - ITT Population							
Time Point	Statistic	Colchicine Dose			Treatment Comparisons <sup>1</sup>		
		High (N = 52)	Low (N = 74)	Placebo (N = 58)	High vs. Placebo	Low vs. Placebo	High vs. Low
24 Hours Post First Dose							
Baseline	Mean (SD)	6.9 (1.59)	6.9 (1.72)	6.8 (1.44)	-1.3	-1.5	0.2
	Median (Mix, Max)	7.0 (4, 10)	7.0 (4, 10)	7.0 (4, 10)	p = 0.0145	p = 0.0055	p = 0.7540
Change	Mean (SD)	-2.0 (2.93)	-2.2 (3.46)	-0.7 (2.77)			
	Median (Mix, Max)	-2.0 (-9, 4)	-2.0 (-9, 5)	-0.0 (-8, 4)			
32 Hours Post First Dose							
Baseline	Mean (SD)	6.9 (1.59)	6.9 (1.72)	6.8 (1.44)	-1.6	-1.6	0.1
	Median (Mix, Max)	7.0 (4, 10)	7.0 (4, 10)	7.0 (4, 10)	p = 0.0057	p = 0.0038	p = 0.9238
Change	Mean (SD)	-2.3 (3.05)	-2.4 (3.59)	-0.7 (2.95)			
	Median (Mix, Max)	-2.0 (-9, 3)	-2.5 (-9, 5)	0.0 (-8, 4)			

<sup>2</sup>Tabled values are the difference between treatment groups mean change from baseline and p-value from ANCOVA with treatment group as the independent variable and baseline score as the covariate.

Total Pain Relief (TOTPAR) Based on All Target Joint Pain Scores				
Time Point	Statistic	Colchicine Dose		
		High (N = 52)	Low (N = 74)	Placebo (N = 58)
Hour 24	n	51 <sup>1</sup>	74	58
	Mean (SD)	20.9 (48.42)	30.5 (61.44)	9.5 (45.87)
	Median (Mix, Max)	11.5 (-102, 135)	23.0 (-112, 185)	7.3 (-90, 142)
Hour 32	n	51	74	58
	Mean (SD)	31.9 (63.83)	45.5 (82.05)	12.2 (59.88)
	Median (Mix, Max)	27.5 (-102, 185)	34.1 (-128, 257)	7.3 (-114, 142)

<sup>1</sup>Patient 1026-1005 did not have a diary and the 24-hour call to the Call Center was 27 hours after the initial call. As indicated in the SAP, the Call Center pain score was not eligible for substitution for the missing diary. This patient has been excluded from the TOTPAR summary.

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Number (%) of Patients Using Rescue Medication Up to and Including the 24-Hour Post First Dose Assessment					
Colchicine Dose					
High (N = 52)	Low (N = 74)	Placebo (N = 58)	Treatment Comparison (Odds Ratio and 95% CI)		
n (%)	n (%)	n (%)	High vs. Placebo	Low vs. Placebo	High vs. Low
18 (34.6)	23 (31.1)	29 (50.0%)	0.53 (0.25, 1.14) p = 0.1034	0.45 (0.22, 0.92) p = 0.0273	1.17 (0.55, 2.50) p = 0.6768

Change from Baseline in Target Joint Pain Scores at 24 Hours Post First Dose with Interval of Time of Dose Relative to Flare Onset as Covariate (LOCF) - ITT Population							
Statistic		Colchicine Dose			Treatment Comparisons <sup>1</sup>		
		High (N = 52)	Low (N = 74)	Placebo (N = 58)	High vs. Placebo	Low vs. Placebo	High vs. Low
Early Treatment Start (within 4 hours)							
Baseline	Mean (SD)	6.9 (1.59)	6.9 (1.72)	6.8 (1.44)	-1.3	-1.5	0.2
	Median (Mix, Max)	7.0 (4, 10)	7.0 (4, 10)	7.0 (4, 10)	p = 0.0145	p = 0.0055	p = 0.7540
Change	Mean (SD)	-2.0 (2.93)	-2.2 (3.46)	-0.7 (2.77)			
	Median (Mix, Max)	-2.0 (-9, 4)	-2.0 (-9, 5)	-0.0 (-8, 4)			
Late Treatment Start (after 4 hours)							
Baseline	Mean (SD)	6.9 (1.59)	6.9 (1.72)	6.8 (1.44)	-1.6	-1.6	0.1
	Median (Mix, Max)	7.0 (4, 10)	7.0 (4, 10)	7.0 (4, 10)	p = 0.0057	p = 0.0038	p = 0.9238
Change	Mean (SD)	-2.3 (3.05)	-2.4 (3.59)	-0.7 (2.95)			
	Median (Mix, Max)	-2.0 (-9, 3)	-2.5 (-9, 5)	0.0 (-8, 4)			

<sup>1</sup>Patient 1016-1013 was missing a flare onset time and Patients 1002-1007, 1018-1008, 1006-1013, 1009-1011, 1010-1005, 1010-1010, 1026-1002, 1026-1007, 1064-1007, and 1068-1022 appear to have taken the first dose of study medication prior to flare onset.

<sup>2</sup>Tabled values are the difference between treatment groups mean change from baseline and p-value from ANCOVA with treatment group as the independent variable and baseline score as the covariate.

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Overall Summary of Treatment Emergent Adverse Events - Safety Population			
Colchicine Dose			
	High (N = 52) n (%)	Low (N = 74) n (%)	Placebo (N = 59) n (%)
Total Number of TEAEs <sup>1</sup>	85	34	27
Number (%) of Patients with at Least One TEAE	40 (76.9)	27 (36.5)	16 (27.1)
Number (%) of Patients with at Least One Mild TEAE	15 (28.8)	19 (25.7)	9 (15.3)
Number (%) of Patients with at Least One Moderate TEAE	15 (28.8)	8 (10.8)	6 (10.2)
Number (%) of Patients with at Least One Severe TEAE	10 (19.2)	0	1 (1.7)

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Overall Summary of Treatment Emergent Adverse Events - Safety Population			
Colchicine Dose			
	High (N = 52) n (%)	Low (N = 74) n (%)	Placebo (N = 59) n (%)
Number (%) of Patients with a TEAE	0	0	0
Discontinuing Study			
Number (%) of Patients with a Treatment Emergent SAE	0	0	0

<sup>1</sup>Patients reporting more than one adverse event are only counted once for a given event.

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Number (%) of Patients with at Least One Treatment-Emergent Gastrointestinal Adverse Event Recorded on the Diary or the CRF- Safety Population						
Method of Capture	Colchicine Dose					
	Standard (N = 52)		Low (N = 74)		Placebo (N = 59)	
	All	Severe	All	Severe	All	Severe
Captured on Adverse Event CRF <sup>1</sup>	40 (76.9) <sup>2</sup>	10 (19.2)	19 (25.7)	0	12 (20.3)	0
Captured on Patient Diary	48 (92.3) <sup>2</sup>	13 (25.0)	32 (43.2) <sup>3</sup>	3 (4.1)	15 (25.4)	2 (3.4)
Captured on Patient Diary or Adverse Event CRF	49 (94.2) <sup>2</sup>	18 (34.6)	33 (44.6)	3 (4.1)	16 (27.1)	2 (3.4)

<sup>1</sup>Gastrointestinal adverse events captured on the AE CRF include the MedDRA preferred terms of "diarrhoea", "nausea", "vomiting", "abdominal pain", or "abdominal pain lower", "abdominal pain upper", "abdominal discomfort", or "dyspepsia".

<sup>2</sup>Statistically significantly different from placebo and from Low-dose colchicine (95% CI of odds ratio does not include "1").

<sup>3</sup>Statistically significantly different from placebo (95% CI of odds ratio does not include "1").

Number (%) of Patients with at Least One Severe TEAE in Any Treatment Group- Safety Population								
MedDRA System Organ Class MedDRA Preferred Term	Colchicine Dose				Odds Ratio (95% Confidence)			
	High (N = 52)		Low (N = 74)		Placebo (N = 59)		High vs. Placebo	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	Low vs. Placebo	High vs. Low
Number of Patients with at Least One Severe TEAE	10 (19.2)	0	10 (7.9)	1 (1.7)	13.8 (1.7, 112)	—	—	—
Gastrointestinal Disorders	10 (19.2)	0	10 (7.9)	0	—	—	—	—
Diarrhea	10 (19.2)	0	10 (7.9)	0	—	—	—	—
Melaena	1 (1.9)	0	1 (0.8)	0	—	—	—	—
Nausea	1 (1.9)	0	1 (0.8)	0	—	—	—	—
Metabolism and Nutrition Disorders	0	0	0	1 (1.7)	—	—	—	—
Gout	0	0	0	1 (1.7)	—	—	—	—
Musculoskeletal and Connective Tissue Disorders	1 (1.9)	0	1 (0.8)	0	—	—	—	—
Pain in Extremity	1 (1.9)	0	1 (0.8)	0	—	—	—	—

Number (%) of Patients with at Least One Drug-Related Treatment Emergent Adverse Events with an Incidence of $\geq 2\%$ of Patients in Any Treatment Group						
MedDRA System Organ Class MedDRA Preferred Term	Colchicine Dose		Placebo (N = 59)	Odds Ratio (95% Confidence Intervals)		
	High (N = 52)	Low (N = 74)		High vs. Placebo	Low vs. Placebo	High vs. Low
Number of Patients with at Least One Drug-Related TEAE	38 (73.1)	21 (28.4)	14 (23.7)	8.7 (3.7, 20.6)	1.3 (0.6, 2.8)	6.9 (3.1, 15.2)
Gastro-intestinal Disorders	38 (73.1)	18 (24.3)	11 (18.6)	11.8 (4.8, 29.0)	1.4 (0.6, 3.3)	8.4 (3.8, 19.0)
Diarrhea	38 (73.1)	16 (21.6)	8 (13.6)	17.3 (6.6, 45.4)	1.8 (0.7, 4.4)	9.8 (4.3, 22.5)
Nausea	7 (13.5)	3 (4.1)	3 (5.1)	2.9 (0.7, 11.9)	0.8 (0.2, 4.1)	3.7 (0.9, 15.0)
Vomiting	8 (15.4)	0	0	—	—	—

As shown in the above tables, standard dose colchicine produced  $\geq 50\%$  pain reduction at 24 hrs without pain rescue in a greater proportion of patients than did placebo (32.7% vs. 15.5%,  $p=0.0343$ ; odds ratio 2.64 (95% CT, 1.06, 6.62), and more gastrointestinal side effects than placebo (73.1% vs.

18.6%, odds ratio 11.8 {95% CI, 4.8, 29.0}), in particular more diarrhea than placebo (73.1% vs. 13.6%, odds ratio 17.3 {95% CI, 6.6, 45.4}). Low dose colchicine also produced  $\geq 50\%$  pain reduction at 24 hrs without pain rescue in a greater proportion of patients than did placebo (37.8% vs.

15.5%,  $p=0.0046$ ; odds ratio 3.31 (95% CI, 1.41, 7.77)), and more gastrointestinal side effects than placebo (24.3% vs. 18.6%, odds ratio 1.4 {95% CI, 0.7 to 11.9}), but did not significantly differ from placebo with respect to diarrhea (21.6% vs. 13.6%, odds ratio 1.8 {95% CI, 0.7 to 4.4}). Severe diarrhea occurred in 19.2% of patients taking high-dose colchicine while not occurring in the low-dose colchicine group. Vomiting occurred in 15.4% of patients taking high-dose colchicine while not occurring in the low-dose colchicine group.

Based on the primary efficacy variable of  $\geq 50\%$  pain reduction at 24 hrs without pain rescue, the proportion of responders to the standard dose and the low dose colchicine regimens was not significantly different ( $p=0.5529$ ). The odds ratio for being a responder to standard dose colchicine vs. being a responder to low dose colchicine was 0.80 (95% CI, 0.38, 1.68). The proportion of patients rescued prior to 24 hours for the standard dose, low dose and placebo were 34.6%, 28.4% and 48.3%, respectively.

FIG. 1 summarizes efficacy data from the trial. FIG. 1 shows the fraction of all patients improved at 24 hrs post-first dose, regardless of pain rescue, as a function of the percent improvement in pain for each of the three treatment methods (standard dose, low dose, placebo). For example, 49% of patients taking the low dose achieved at least 40% relief compared to 24% of the patients on placebo.

Standard dose oral colchicine was established to be effective, but burdened by significant diarrhea. In contrast, although low dose colchicine was not significantly different from standard dose colchicine in efficacy, low dose colchicine was not significantly different from placebo with respect to diarrhea. This trial provides a new evidence basis for acute gout treatment, specifically supporting the unexpected superiority of a low dose colchicine dosing regimen of 2 tablets of 0.6 mg followed in 1 hour by 1 tablet. The higher standard dose colchicine dosing regimen did not improve patient outcome, but did increase adverse events.

Example 4

Pharmacokinetic Study in Healthy Adults of Single vs. Multiple Oral Doses of Colchicine Tablets

This study was a single-center, open-label, single-sequence, two-period study to evaluate the pharmacokinetic profile of colchicine following single and multiple oral doses of colchicine tablets, 0.6 mg, in healthy volunteers.

In Period 1, study subjects received a 0.6-mg dose of colchicine after an overnight fast of at least 10 hours. In Period 2, subjects received a 0.6-mg dose of colchicine in the morning and the evening (approximately 12 hours later) for 10 days (steady state regimen). Subjects received a light breakfast served 60 minutes following dose administration in the morning and the evening dose was administered 90 minutes after an evening meal on Days 15 through 24 only. On Day 25, the colchicine dose was administered after an overnight fast of at least 10 hours and lunch was served 4 hours post-dose. Study periods were separated by a 14-day wash-out. Following the single dose and the last dose of the multiple dose regimen (beginning on the mornings of Day 1 and Day 25, respectively), blood samples were collected (6 mL each) from each subject within 1 hour prior to dosing and after dose administration at study hours 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 (while confined) and 36, 48, 72, and 96 (on an outpatient basis). Plasma concentrations of colchicine and its metabolites were determined using validated LC/MS-MS methods.

Thirteen healthy, non-smoking subjects with a mean age of 25.5 years (range 19 to 38 years) and within 15% of ideal body weight were enrolled in this study. All subjects completed both dosing periods according to protocol.

After a single dose, plasma concentrations are no longer quantifiable 24 hours post-dose in all but 1 subject. After the last dose of the steady state regimen, concentrations remained quantifiable for 48 to 72 hours. Review of individual subject data shows that no subject experienced a secondary colchicine peak, either following a single dose or upon multiple dosing.

All 2-O-demethylcolchicine (2-DMC) concentrations were below the level of quantitation (LOQ, 0.2 ng/mL) and only one sample from 1 subject (of 13 subjects) had a detectable 3-O-demethylcolchicine (3-DMC) concentration which was near the level of quantitation. Therefore, metabolites are not discussed further.

In healthy adults, colchicine appears to be readily absorbed when given orally, reaching a mean maximum plasma concentration of 2.5 ng/mL in 1.5 hours after a single dose. The drug is distributed widely, with an apparent volume of distribution of 540 L, greatly exceeding total body water. The elimination half-life as calculated following a single oral dose is approximately 5 hours. Levels were not detectable by 24 hours post-dose and this is therefore not an accurate estimate. Pharmacokinetic parameter values are summarized in the table below.

Review of trough plasma concentrations indicates that steady state was attained by approximately the eighth day of dosing for most subjects. Colchicine may have a diurnal variation reflected in the observed Cmin concentrations at steady state. Cmin concentrations prior to the morning dose are approximately 12% higher than the Cmin concentrations prior to the evening dose (Day 23 and Day 24). The mean Cmin concentration observed on Day 25 was 0.907 ng/mL.

Colchicine accumulated following administration of multiple doses to an extent greater than expected. Exposure was nearly two-fold higher (approximately 1.7 based on AUC [Day 25 AUC<sub>0-∞</sub>/Day 1 AUC<sub>0-∞</sub>] and approximately 1.5 based on C<sub>max</sub>[Day 25 C<sub>max</sub>/Day 1 C<sub>max</sub>]). This observation could be attributable to an underestimation of AUC<sub>∞</sub> following a single dose. With the higher plasma levels that occur with repeated dosing, a longer terminal elimination half life is apparent, 26.6 hours. Pharmacokinetic parameter values are summarized in the tables below.

TABLE 10

Colchicine Pharmacokinetic Parameter Values Following Administration of A Single Oral Dose of Colchicine 0.6 mg in Healthy Adults						
	AUC <sub>0-t</sub> (pg-hr/mL)	AUC <sub>0-inf</sub> (pg-hr/mL)	C <sub>max</sub> (pg/mL)	T <sub>max</sub> (hr)	Kel (1/hr)	T <sub>1/2</sub> (hr)
N	13	13	13	13	13	13
MEAN	10508.54	12281.90	2470.77	1.50	0.1829	4.95
STDEV	3544.82	4423.34	706.98	0.54	0.0592	4.43
% CV	33.73	36.02	28.61	36.00	32.39	89.54
MEDIAN	10560.90	11451.45	2714.00	1.50	0.1992	3.48
MIN	4812.88	7252.66	1584.00	1.00	0.0359	2.84
MAX	18128.65	23838.48	3977.00	3.00	0.2443	19.29

TABLE 11

Colchicine Pharmacokinetic Parameter Values Following Administration of Multiple (b.i.d.) Oral Doses of Colchicine 0.6 mg in Healthy Adults								
	AUC <sub>0-t</sub> (pg-hr/mL)	AUC <sub>0-τ</sub> (pg-hr/mL)	AUC <sub>0-inf</sub> (pg-hr/mL)	C <sub>max</sub> (pg/mL)	C <sub>min</sub> (pg/mL)	C <sub>ave</sub> (pg/mL)	T <sub>max</sub> (hr)	T <sub>1/2</sub> (hr)
N	13	13	13	13	13	13	13	13
MEAN	43576.96	29056.23	54198.77	3553.15	906.51	1210.68	1.31	0.03
STDEV	9333.26	4531.30	9214.54	843.45	152.19	188.80	0.60	0.00
% CV	21.42	15.59	17.00	23.74	16.79	15.59	45.61	16.34
MEDIAN	41925.10	28452.15	54113.43	3734.00	903.50	1185.51	1.00	0.03
MIN	29328.78	20791.98	37599.76	1977.00	636.23	866.33	0.50	0.02
MAX	58265.35	36083.95	67944.65	4957.00	1149.67	1503.50	3.00	0.03

TABLE 12

Mean (% CV) Colchicine Pharmacokinetic Parameter Values Following Administration of Single and Multiple (b.i.d.) Oral Doses of Colchicine 0.6 mg in Healthy Adults		
	V <sub>d</sub> /F (L)	CL/F (L/hr)
Colchicine 0.6-mg Single Dose (N = 13)		
Day 1	341 (54.4)	54.1 (31.0)
Colchicine 0.6 mg b.i.d. × 10 days		
Day 25	1150 (18.73)	30.3 (19.0)

CL = Dose/AUC<sub>0-t</sub> (Calculated from mean values)  
V<sub>d</sub> = CL/Ke (Calculated from mean values)

In the above table, the parameter CL/F denotes the apparent total body clearance after administration, calculated as Total Dose/Total AUC<sub>0-t</sub>; and V<sub>d</sub>/F denotes the apparent total volume of distribution after administration, calculated as Total Dose/(Total AUC<sub>∞</sub> × K<sub>el</sub>).

Example 5

Pharmacokinetic Study in Healthy Adults of Low Dose Acute Gout Regimen: 1.8 mg Over 2 Hours

This study was a single-center, single-period, open-label pharmacokinetic study conducted in healthy subjects under

later. Blood samples for measurement of colchicine plasma concentrations and metabolites were collected (relative to the first dose of study drug) at pre-dose; 0.5 and 1 hour post-dose (prior to second dose); and 1.5, 2, 2.5, 3, 4, 6, 8, 12, 18, 24, 36, and 48 hours post-dose. Subjects were confined until 48 hours post-dose and then returned 72 and 96 hours after the first dose for additional blood sampling on an outpatient basis. Plasma concentrations of colchicine and its metabolites were determined using validated LC/MS-MS methods.

2-DMC concentrations were below the LOQ for all subjects. Eight of 13 subjects had at least one measurable 3-DMC concentration (29 total 3-DMC measurable concentrations). 3-DMC concentrations ranged from 0.20 ng/mL (near the LOQ) to 0.45 ng/mL and were observed 1 to 4 hours post-dose. Given these low levels, metabolites are not discussed further herein.

When colchicine was administered in this low-dose regimen, concentrations increased to a maximum of 6.2 ng/mL, occurring 1.81 hours after the initial dose (0.81 hours after the second dose). Most of the subjects (10 of 13 subjects or 77%) experienced a secondary peak within 6 hours after the first of the two doses, attributed to intestinal secretion and re-absorption and/or biliary recirculation.

The terminal elimination half-life was 23.6 hours. A summary of the pharmacokinetic parameter values is provided in the table below.

TABLE 12

COLCHICINE PHARMACOKINETIC PARAMETER VALUES AFTER LOW-DOSE COLCHICINE (1.8 MG OVER 2 HOURS) ADMINISTRATION IN HEALTHY ADULTS								
	C <sub>max</sub> (pg/mL)	T <sub>max</sub> (hr)	Total AUC <sub>0-t</sub> (pg-hr/mL)	Total AUC <sub>∞</sub> (pg-hr/mL)	K <sub>el</sub> (1/hr)	CL/F (mL/hr)	V <sub>d,area</sub> /F (L)	t <sub>1/2</sub> (hr)
N	13	13	13	13	13	13	13	13
MEAN	6192.77	1.81	43787.55	52070.06	0.0326	36950.93	1188.72	23.63
STDEV	2433.70	0.38	11437.48	13689.27	0.0100	9993.17	319.56	9.24
% CV	39.30	21.24	26.12	26.29	30.80	27.04	26.88	39.10
MEDIAN	5684.00	2.00	43942.15	50783.77	0.0322	35444.40	1149.35	21.56
MIN	3160.00	1.00	28821.45	34171.00	0.0141	24295.73	774.19	13.80
MAX	11370.00	2.50	58931.99	74087.08	0.0502	52676.24	1724.36	49.20

fasting conditions. It was designed to characterize the pharmacokinetic profile of a low-dose regimen of colchicine (1.8 mg over 2 hours) used as one of the treatment arms in the randomized, controlled trial in patients with an acute gout flare discussed above.

Thirteen healthy, non-smoking subjects with a mean age of 29.3 years (range 20 to 49 years) and within 15% of ideal body weight were enrolled in this study. Subjects received 2×0.6 mg tablets initially followed by 1×0.6 mg tablet 1 hour

Example 6

Pharmacokinetic Study in Healthy Adults of a Standard-Dose Acute Gout Regimen: 4.8 mg Colchicine Over 6 Hours.

This study was a single center, randomized, double-blind, double-dummy pharmacokinetic and exploratory ECG safety study.

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With respect to the pharmacokinetic aspect of the study, on Day 1, following a minimum of 10 hours overnight fast, subjects received the appropriate randomized study drug (combination of over-encapsulated active drug or placebo capsules such that the blind was preserved). Those randomized to colchicine received 4.8 mg over 6 hours (initially 2x0.6 mg tablets followed by 1x0.6 mg tablet every hour for six additional doses). Those randomized to moxifloxacin received 1x400 mg tablet. Both dosing regimens were followed by a 4-hour post-dose fast (post-dose fast for colchicine arm started after the first dose of colchicine administered). Blood samples were obtained on Day 1 at the following time points (relative to the first dose of study drug): pre-dose and 1 (prior to second dose), 3 (prior to fourth dose), 6 (prior to final dose), 6.17, 6.33, 6.5, 6.75, 7, 7.25, 7.5, 7.75, 8, 10, 12, 23, 36, 48, 72 and 96 hours post-dose. Subjects were confined until 48 hours post-dose and then returned 72 and 96 hours after the first dose for additional blood sampling on an outpatient basis. Plasma concentrations of colchicine and its metabolites were determined using validated LC/MS-MS methods.

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Eighteen healthy, non-smoking subjects with a mean age of 28.7 years (range 18 to 50 years) and within 15% of ideal body weight were enrolled in this study. Fifteen subjects were randomized to receive colchicine and 3 subjects were randomized to receive moxifloxacin as a positive control for QTc prolongation. All subjects completed the study according to protocol.

When colchicine was administered as the standard-dose regimen used in the treatment of patients experiencing an acute gout flare, colchicine concentrations increased to a maximum of 6.8 ng/mL (similar to the reported C<sub>max</sub> in the low-dose regimen) and absorbed approximately 4.5 hours after the initial dose (3.5 hours after the second dose). Most of the subjects (13 of 15 subjects receiving colchicine or 87%) experienced a secondary peak within 6 hours after a single oral dose, attributed to intestinal secretion and re-absorption and/or biliary recirculation. The terminal elimination half-life was 31.38 hours. A summary of the pharmacokinetic parameter values is provided in the table below.

TABLE 13

MEAN (% CV) COLCHICINE PHARMACOKINETIC PARAMETER VALUES AFTER STANDARD-DOSE COLCHICINE (4.8 MG OVER 6 HOURS) ADMINISTRATION IN HEALTHY ADULTS								
	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (hr)	Total AUC <sub>0-t</sub> (ng-hr/mL)	Total AUC <sub>∞</sub> (ng-hr/mL)	K <sub>el</sub> (h <sup>-1</sup> )	CL/F (mL/hr)	V <sub>area</sub> /F (L)	t <sub>1/2</sub> (hr)
N	15	15	15	15	15	15	15	15
MEAN	6.84	4.47	104.95	118.20	0.0242	43168.87	1876.09	31.38
STDEV	1.30	1.99	24.61	26.01	0.0088	12862.03	456.19	8.36
% CV	18.94	44.65	23.45	22.01	36.59	29.79	24.32	26.65
MEDIAN	6.69	3.12	113.12	126.47	0.0212	37954.71	1902.14	32.76
MIN	4.95	3.12	53.74	61.31	0.0147	31386.01	805.92	15.03
MAX	8.60	7.50	138.24	152.93	0.0461	78287.41	2639.21	47.22

2-DMC concentrations were below LOQ for all subjects. Fourteen of 15 subjects had at least one measurable 3-DMC concentration; the 3-DMC concentrations ranged from 0.25 ng/mL (near the LOQ) to 0.42 ng/mL and were observed 1.12 to 12.12 hours post-dose. Summary mean 3-DMC pharmacokinetic parameter values can be found in the table below. The observed mean 3-DMC C<sub>max</sub>, AUC<sub>0-t</sub>, and AUC<sub>∞</sub> concentrations were approximately 4.7%, 2%, and 4.1% of the observed mean colchicine C<sub>max</sub>, AUC<sub>0-t</sub>, AUC<sub>∞</sub> concentrations, respectively.

TABLE 14

Mean (% CV) 3-DMC Pharmacokinetic Parameter Values after Standard-Dose Colchicine (4.8 mg over 6 hours) Administration in Healthy Adults						
	C <sub>max</sub> (ng/mL)	T <sub>max</sub> <sup>1</sup> (h)	AUC <sub>0-t</sub> (ng · h/mL)	AUC <sub>∞</sub> (ng · h/mL)	Ke (h <sup>-1</sup> )	t <sub>1/2</sub> (h)
	N = 15	N = 14	N = 13	N = 8	N = 8	N = 8
Standard Dose	0.32	5.06	2.09	4.84	0.1418	6.93
N = 15	(16.35)	(3.12-8.12)	(40.29)	(42.73)	(60.15)	(64.35)

<sup>1</sup>T<sub>max</sub> reported mean (range)

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## Example 7

Food Effect Study Single Dose Vs.  
COL-Probenecid® (0.5 MG Colchicine/500 MG  
Probenecid)

The clinical study of this example was a randomized, single-dose, three-way crossover study testing the bioequivalence of two formulations of colchicine administered under standard fasting conditions, one the 0.6 mgA colchicine formulation of Example 2 (test product) and one a marketed combination product, 0.5 mg colchicine/500 mg probenecid tablets (COL-PROBENECID®, Watson Laboratories, Inc.) (reference product), and the effect of food on the test product by dosing following a high-fat breakfast.

Twenty-eight healthy non-smoking adult volunteers (male and female) and no alternates initiated the study. Subjects received three single doses, in a randomized sequence of three treatment periods. On each occasion, subjects received either one colchicine tablet USP, 0.6 mg (test product) given either with food or in a standard fasting condition or one colchicine 0.5 mg/probenecid 500 mg tablet (reference product) given in a standard fasting condition. Each treatment period was separated by a 14-day washout.

The two dosing conditions were (1) Standard Fasting Conditions (either colchicine tablets USP, 0.6 mg (test A) or reference product, COL-PROBENECID®): 1 tablet of test product (Test A) or reference product with 240 mL of room temperature water after an overnight fast of at least 10 hours; subjects will continue to fast for 4 hours post-dose; and (2)

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dard meal) depending on the randomization, was allowed from 1 hour prior to dose administration until 2 hours after dosing. When fluids were restricted, they will be allowed ad libitum but will generally be controlled.

5 Dinner was served approximately 13.5 hours prior to dose administration. At 30 minutes before dose administration, those subjects to be dosed after eating (depending on randomization) were served the standardized, high-fat and high-calorie breakfast (FDA standard meal). All subjects fasted for at least 4 hours after dosing. Clear fluids, such as water, were allowed during fasting.

Subjects were served standardized meals and beverages, controlled by the clinic during periods of confinement. Meals were the same in content and quantity during each confinement period. No grapefruit and/or grapefruit containing products or caffeine and/or xanthine containing products were allowed during the confinement portions of the study.

During confinement, only non-strenuous activity was permitted. Following dose administration, subjects remained in a seated or upright position for at least 4 hours to ensure proper gastric emptying and subject safety.

Blood (6 mL) was collected in K2 EDTA vacutainers with samples taken within 1 hour prior to dosing (0 hour) and after dose administration at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours (while confined) and 36, 48, 72, and 96 hours (on an outpatient basis). 1. Colchicine and metabolite plasma concentrations (colchicine, 2-DMC, 3-DMC, and 10 demethylcolchicine) were measured using a validated bioanalytical method.

Pharmacokinetic results comparing the test product under fed and fasting conditions are shown below.

TABLE 15

Pharmacokinetic results of colchicine test product under fed and fasting						
Ln-Transformed Data						
PK Variable	Least Squares Mean		Geometric Mean		90% Confidence Interval	
	Test B	Test A	Test B	Test A	% Ratio	(Lower Limit, Upper Limit)
$C_{max}$ (ng/mL)	7.784	7.781	2402.55	2393.60	100.37	(89.84, 112.14)
$AUC_{0-t}$ (ng/mL-hr)	9.201	9.334	9906.40	11310.90	87.58	(78.07, 98.26)
$AUC_{0-inf}$ (ng/mL-hr)	9.300	9.468	10939.73	12939.64	84.54	(76.73, 93.15)
Geometric means are based on least squares means of ln-transformed values.						
Non-Transformed Data						
PK Variable	Least Squares Mean			90% Confidence Interval		
	Test B	Test A	% Ratio	(Lower Limit, Upper Limit)		
$C_{max}$ (pg/mL)	2486.99	2493.15	99.75	(90.43, 109.07)		
$AUC_{0-t}$ (pg/mL-hr)	10438.89	12536.56	83.27	(72.79, 93.74)		
$AUC_{0-inf}$ (pg/mL-hr)	11345.62	13907.83	81.58	(71.53, 91.63)		
$T_{max}$ (hr)	1.85	1.35	137.14	(111.11, 163.17)		
$K_{el}$ (hr <sup>-1</sup> )	0.1902	0.1520	125.13	(107.67, 142.58)		
$T_{1/2}$ (hr)	4.34	6.27	69.17	(45.2, 93.14)		

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High-fat Breakfast (colchicine tablets USP, 0.6 mg): 1 tablet of test product (Test B) with 240 mL of room temperature water 30 minutes after initiation of a standardized, high-fat and high-calorie breakfast (FDA standard meal) preceded by an overnight fast.

Subjects were confined for at least 15 hours prior to and until at least 24 hours after dosing each period. During each period, subjects returned on four separate occasions for outpatient blood sampling.

No fluid, except that given with drug administration and the standardized high-fat and high-calorie breakfast (FDA stan-

TABLE 16

Descriptive statistics for Pharmacokinetic Parameters for Test Product A (0.6 mg) - Fasting conditions			
	$AUC_{0-t}$ (pg-hr/mL)	$AUC_{0-inf}$ (pg-hr/mL)	$C_{max}$ (pg/mL)
N	25	24	25
Arithmetic Mean	12589	14113	2503
STDev	6210.729	5595.398	722.049
% CV	48.621	39.648	28.847

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TABLE 16-continued

Descriptive statistics for Pharmacokinetic Parameters for Test Product A (0.6 mg) - Fasting conditions			
	AUC <sub>0-t</sub> (pg-hr/mL)	AUC <sub>0-inf</sub> (pg-hr/mL)	C <sub>max</sub> (pg/mL)
Median	11412.80	12756.02	2473.00
Min	4430.73	6674.96	1291.00
Max	30787.30	27789.51	3989.00

TABLE 17

Descriptive statistics for Pharmacokinetic Parameters for Test Product A (0.6 mg) - Fed conditions			
	AUC <sub>0-t</sub> (pg-hr/mL)	AUC <sub>0-inf</sub> (pg-hr/mL)	C <sub>max</sub> (pg/mL)
N	25	22	25
Arithmetic Mean	10491	11404	2497
STDev	4024.804	2895.681	695.091
% CV	38.374	25.392	27.838
Median	9556.25	10964.17	2293.00
Min	6168.53	7128.50	1256.00
Max	26031.15	20101.33	3930.00

Food was observed to have negligible effect on rate of absorption, as indicated by the percent ratio of ln-transformed C<sub>max</sub> data of 100.37, but decreased the extent of absorption by about 15%, as indicated by the percent ratio of ln-transformed AUC<sub>0-t</sub> and AUC<sub>0-inf</sub> values of 87.56 and 84.54, respectively. Under fasted and fed conditions, the mean C<sub>max</sub> was 2.5 ng/mL. T<sub>max</sub> was 1.35 hrs under fasted conditions and 1.85 hrs under fed conditions.

Pharmacokinetic results comparing the test product to the reference product are shown in the tables below. The difference in colchicine potency of the test and reference products was corrected by calculating dose-normalized values in the pharmacokinetic parameters.

TABLE 18

Summary of Statistical Analysis Colchicine Test Product A (0.6 mg) - Fasting vs Reference Product C (0.5 mg) - Fasting (Dose Normalized to 0.5 mg) N = 25						
Ln-Transformed Data						
PK Variable	Least Squares Mean		Geometric Mean		90% Confidence Interval	
	Test A	Reference C	Test A	Reference C	% Ratio	(Lower Limit, Upper Limit)
C <sub>max</sub> (ng/mL)	7.598	7.374	1994.67	1594.51	125.10	(111.97, 139.76)
AUC <sub>0-t</sub> (ng/mL-hr)	9.151	8.833	9425.75	6858.61	137.43	(122.5, 154.18)
AUC <sub>0-inf</sub> (ng/mL-hr)	9.286	8.970	10783.03	7863.34	137.13	(124.46, 151.09)

Geometric means are based on least squares means of ln-transformed values.

Non-Transformed Data						
PK Variable	Least Squares Mean		Geometric Mean		90% Confidence Interval	
	Test A	Reference C	Test A	Reference C	% Ratio	(Lower Limit, Upper Limit)
C <sub>max</sub> (pg/mL)	2076.08	1688.54	122.95	110.07	135.83	(110.07, 135.83)
AUC <sub>0-t</sub> (pg/mL-hr)	10435.91	8016.44	130.18	115.25	145.11	(115.25, 145.11)
AUC <sub>0-inf</sub> (pg/mL-hr)	11565.28	8230.68	140.51	126.04	154.99	(126.04, 154.99)
T <sub>max</sub> (hr)	1.35	1.34	100.11	74.05	126.17	(74.05, 126.17)
K <sub>el</sub> (hr <sup>-1</sup> )	0.1520	0.1970	77.16	63.69	90.63	(63.69, 90.63)
T <sub>1/2</sub> (hr)	6.27	3.78	165.89	126.13	205.65	(126.13, 205.65)

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The 0.6 mgA colchicine tablet, formulated as in Example 2, showed enhanced bioavailability over COL-PROBENECID®. The formulation disclosed herein showed a greater rate and extent of absorption than did the COL-PROBENECID®.

Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. The endpoints of all ranges directed to the same component or property are inclusive and independently combinable.

All methods described herein can be performed in a suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") provided herein, is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the invention as used herein. Unless defined otherwise, technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs. The terms wt %, weight percent, percent by weight, etc. are equivalent and interchangeable.

Embodiments of this invention are described herein, including the best mode known to the inventors for carrying out the invention. Variations of those preferred embodiments may become apparent to those of ordinary skill in the art upon reading the foregoing description. The inventors expect skilled artisans to employ such variations as appropriate, and the inventors intend for the invention to be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is

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encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.

I claim:

1. A method of treating a patient having an acute gouty arthritis attack with colchicine consisting of

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administering 1.2 mg oral colchicine to a human patient having an acute gouty arthritis attack at the onset of the acute gouty arthritis attack, followed by 0.6 mg oral colchicine one hour later.

\* \* \* \* \*

UNITED STATES PATENT AND TRADEMARK OFFICE  
**CERTIFICATE OF CORRECTION**

PATENT NO. : 7,964,647 B2  
APPLICATION NO. : 12/407980  
DATED : June 21, 2011  
INVENTOR(S) : Matthew W. Davis

Page 1 of 2

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In column 5, line 41, delete “mitotis,” and insert -- mitosis, --, therefor.

In column 10, line 4, delete “and HPLC” and insert -- and UPLC --, therefor.

In column 10, line 41, delete “(HPLC)” and insert -- (UPLC) --, therefor.

In column 12, line 42, delete “calorimetric” and insert -- colorimetric --, therefor.

In column 13, line 44, after “manufacture” insert -- . --.

In column 13, line 66, delete “N-formyldeactylcholchicine,” and insert  
-- N-formyldeacetylcolchicine, --, therefor.

In column 15, line 42, delete “AVICELL®” and insert -- AVICEL® --, therefor.

In column 15, line 55, after “composition” insert -- . --.

In column 15, line 61, delete “alignates,” and insert -- alginates, --, therefor.

In column 16, line 14-15, delete “crosscarmellose” and insert -- croscarmellose --, therefor.

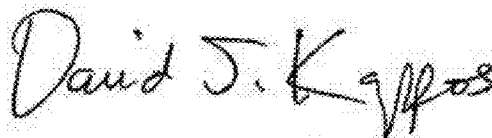
In column 18, line 5, delete “or HPLC” and insert -- or UPLC --, therefor.

In column 20, line 32, after “0.5%” insert -- . --.

In column 21, line 59, delete “methanl” and insert -- methanol --, therefor.

In column 22, line 29, delete “Volumentric” and insert -- Volumetric --, therefor.

Signed and Sealed this  
Fifteenth Day of November, 2011

A handwritten signature in black ink, reading "David J. Kappos". The signature is written in a cursive, flowing style with a large initial "D".

David J. Kappos  
*Director of the United States Patent and Trademark Office*

**CERTIFICATE OF CORRECTION (continued)**

Page 2 of 2

**U.S. Pat. No. 7,964,647 B2**

In column 22, line 33, delete “Volumetric” and insert -- Volumetric --, therefor.

In column 28, line 49, delete “probenicid.” and insert -- probenicid. --, therefor.

In column 37-38, line 31, delete “goup” and insert -- group --, therefor.

In column 41, line 66, delete “CT,” and insert -- CI, --, therefor.

In column 44, line 16, delete “demethylcolchicine” and insert -- demethylcolchicine --, therefor.

In column 52, line 26, after “interchangeable” insert -- . --.

UNITED STATES PATENT AND TRADEMARK OFFICE  
**CERTIFICATE OF CORRECTION**

PATENT NO. : 7,964,647 B2  
APPLICATION NO. : 12/407980  
DATED : June 21, 2011  
INVENTOR(S) : Matthew W. Davis

Page 1 of 3

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On Title Page 2, Item (56), Col. 2, line 6, delete “CColchicine” and insert -- Colchicine --, therefor.

In column 3, line 14, delete “Cmax” and insert --  $C_{\max}$  --, therefor.

In column 4, line 17, delete “Cmax” and insert --  $C_{\max}$  --, therefor.

In column 4, line 28, delete “(AUC<sub>0-∞</sub>INF)” and insert -- (AUC<sub>0-∞</sub>) --, therefor.

In column 4, line 32, delete “Cmax” and insert --  $C_{\max}$  --, therefor.

In column 4, line 42, delete “Cmax” and insert --  $C_{\max}$  --, therefor.

In column 4, line 43, delete “Cmax” and insert --  $C_{\max}$  --, therefor.

In column 6, line 42, delete “AUC<sub>1-t</sub>” and insert -- AUC<sub>0-t</sub> --, therefor.

In column 6, line 64, delete “0.010%” and insert -- 0.10% --, therefor.

In column 7, line 61, delete “asparagin-” and insert -- asparagin- --, therefor.

In column 7, line 67, delete “asparinate” and insert -- asparinate --, therefor.

In column 17, line 54, delete “Impurity B.” and insert -- Impurity B, --, therefor.

In column 21, line 43, after “USP/30NF25” insert -- . --.

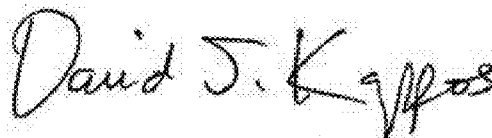
In column 28, line 49, delete “probenicid” and insert -- probenecid --, therefor.

In column 30, line 35, delete “14” and insert -- 14 --, therefor.

In column 31, line 7, delete “levels to undetectable” and insert -- undetectable --, therefor.

In column 33, line 56, delete “also be,” and insert -- also --, therefor.

Signed and Sealed this  
Third Day of July, 2012

A handwritten signature in black ink, reading "David J. Kappos". The signature is written in a cursive, flowing style with a large initial "D".

David J. Kappos  
*Director of the United States Patent and Trademark Office*

**CERTIFICATE OF CORRECTION (continued)**

Page 2 of 3

**U.S. Pat. No. 7,964,647 B2**

In column 37, line 49, delete “<sup>2</sup>Tabled” and insert -- <sup>1</sup>Tabled --, therefor.

In column 39, line 46, delete “<sup>1</sup>Patient” and insert -- Patient --, therefor.

In column 39, line 48, delete “<sup>2</sup>Tabled” and insert -- <sup>1</sup>Tabled --, therefor.

In column 44, line 34, delete “Cmin” and insert -- C<sub>min</sub> --, therefor.

In column 44, line 35, delete “Cmin” and insert -- C<sub>min</sub> --, therefor.

In column 44, line 36, delete “Cmin” and insert -- C<sub>min</sub> --, therefor.

In column 44, line 38, delete “Cmin” and insert -- C<sub>min</sub> --, therefor.

In column 44, line 56, delete “Kel” and insert -- K<sub>el</sub> --, therefor.

In column 45, line 16, after “Table 12” insert -- A --.

In column 45, line 21, delete “Vd” and insert -- V<sub>d</sub> --, therefor.

In column 45, line 28, delete “Vd = CL/Ke” and insert -- V<sub>d</sub> = CL/K<sub>e</sub> --, therefor.

In column 46, line 5, delete “Kel” and insert -- K<sub>el</sub> --, therefor.

In column 46, line 43, after “Table 12” insert -- B --.

In column 48, line 13, delete “Cmax” and insert -- C<sub>max</sub> --, therefor.

In column 48, line 48, delete “Cmax” and insert -- C<sub>max</sub> --, therefor.

In column 48, line 48, delete “AUC∞” and insert -- AUC<sub>∞</sub> --, therefor.

In column 48, line 50, delete “Cmax” and insert -- C<sub>max</sub> --, therefor.

In column 48, line 50, delete “AUC∞” and insert -- AUC<sub>∞</sub> --, therefor.

In column 48, line 58, delete “Ke” and insert -- K<sub>e</sub> --, therefor.

In column 49, line 41, delete “ng” and insert -- pg --, therefor.

In column 49, line 42, delete “ng” and insert -- pg --, therefor.

In column 49, line 43, delete “ng” and insert -- pg --, therefor.

In column 49, line 51, delete “Kel” and insert -- K<sub>el</sub> --, therefor.

In column 50, line 44, delete “In-transformed” and insert -- ln-transformed --, therefor.

In column 50, line 61, delete “AUC0-t” and insert -- AUC<sub>0-t</sub> --, therefor.

**CERTIFICATE OF CORRECTION (continued)**

Page 3 of 3

**U.S. Pat. No. 7,964,647 B2**

In column 50, line 62, delete “AUC0-inf” and insert --  $AUC_{0-inf}$  --, therefor.

In column 50, line 62, delete “Cmax” and insert --  $C_{max}$  --, therefor.

In column 51, line 5, delete “AUC0-t” and insert --  $AUC_{0-t}$  --, therefor.

In column 51, line 6, delete “AUC0-inf” and insert --  $AUC_{0-inf}$  --, therefor.

In column 51, line 6, delete “Cmax” and insert --  $C_{max}$  --, therefor.

In column 51, line 17, delete “AUC0-t” and insert --  $AUC_{0-t}$  --, therefor.

In column 51, line 18, delete “AUC0-inf” and insert --  $AUC_{0-inf}$  --, therefor.

In column 51, line 18, delete “Cmax” and insert --  $C_{max}$  --, therefor.

In column 51, line 28, delete “Cmax” and insert --  $C_{max}$  --, therefor.

In column 51, line 29, delete “In-trans-” and insert -- ln-trans- --, therefor.

In column 51, line 30, delete “AUC0-t” and insert --  $AUC_{0-t}$  --, therefor.

In column 51, line 30, delete “AUC0-inf” and insert --  $AUC_{0-inf}$  --, therefor.

In column 51, line 31, delete “Cmax” and insert --  $C_{max}$  --, therefor.

In column 51, line 32, delete “Tmax” and insert --  $T_{max}$  --, therefor.

In column 51, line 49, delete “ng” and insert -- pg --, therefor.

In column 51, line 50, delete “ng” and insert -- pg --, therefor.

In column 51, line 51, delete “ng” and insert -- pg --, therefor.

In column 51, line 63, delete “Kel” and insert --  $K_{el}$  --, therefor.

# EXHIBIT D

US007964648B2

(12) **United States Patent**  
**Davis**(10) **Patent No.:** **US 7,964,648 B2**  
(45) **Date of Patent:** **\*Jun. 21, 2011**(54) **METHODS FOR CONCOMITANT  
ADMINISTRATION OF COLCHICINE AND A  
SECOND ACTIVE AGENT**(75) Inventor: **Matthew W. Davis**, Erwinna, PA (US)(73) Assignee: **Mutual Pharmaceutical Company,  
Inc.**, Philadelphia, PA (US)(\*) Notice: Subject to any disclaimer, the term of this  
patent is extended or adjusted under 35  
U.S.C. 154(b) by 0 days.This patent is subject to a terminal dis-  
claimer.(21) Appl. No.: **12/688,038**(22) Filed: **Jan. 15, 2010**(65) **Prior Publication Data**

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Feb. 17, 2009.(60) Provisional application No. 61/152,067, filed on Feb.  
12, 2009, provisional application No. 61/138,141,  
filed on Jan. 14, 2009.(51) **Int. Cl.**

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<b>C07C 205/00</b>	(2006.01)
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568/306; 514/254.07; 514/254.1; 514/396(58) **Field of Classification Search** ..... 514/629,  
514/254.7, 254.1, 396; 564/123, 308, 427;  
568/306

See application file for complete search history.

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*Primary Examiner* — Sreeni Padmanabhan*Assistant Examiner* — Kara R McMillian(74) *Attorney, Agent, or Firm* — Cantor Colburn LLP(57) **ABSTRACT**Methods for concomitant administration of colchicine  
together with one or more second active agents, e.g., keto-  
conazole and ritonavir, are disclosed. Such methods reduce  
the dangers commonly associated with such concomitant  
administration and provide additional benefits. Methods of  
notifying health care practitioners and patients regarding  
appropriate dosing for concomitant administration of colchi-  
cine together with second active agents are also provided.**8 Claims, 5 Drawing Sheets**

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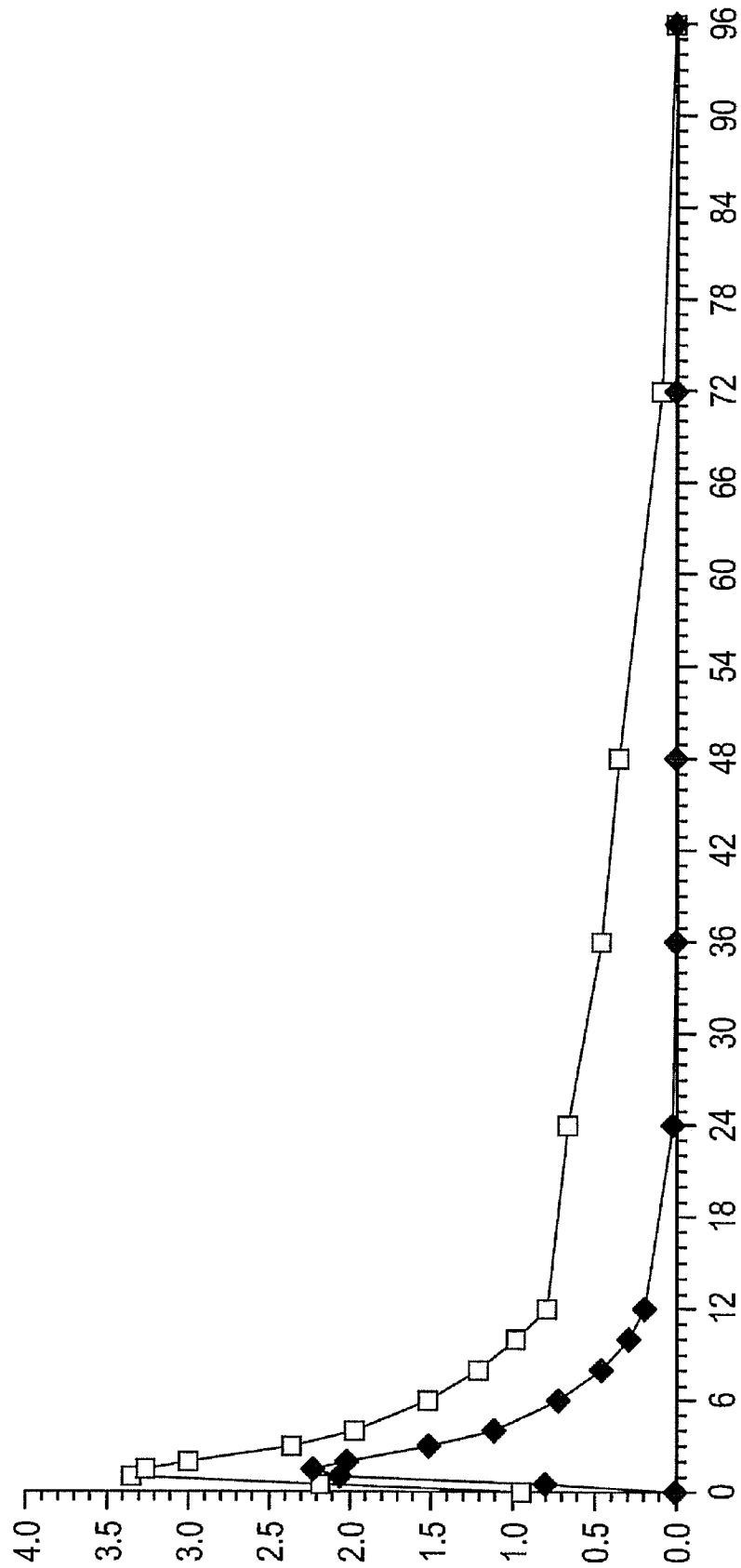
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**FIG. 1**



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**FIG. 2**

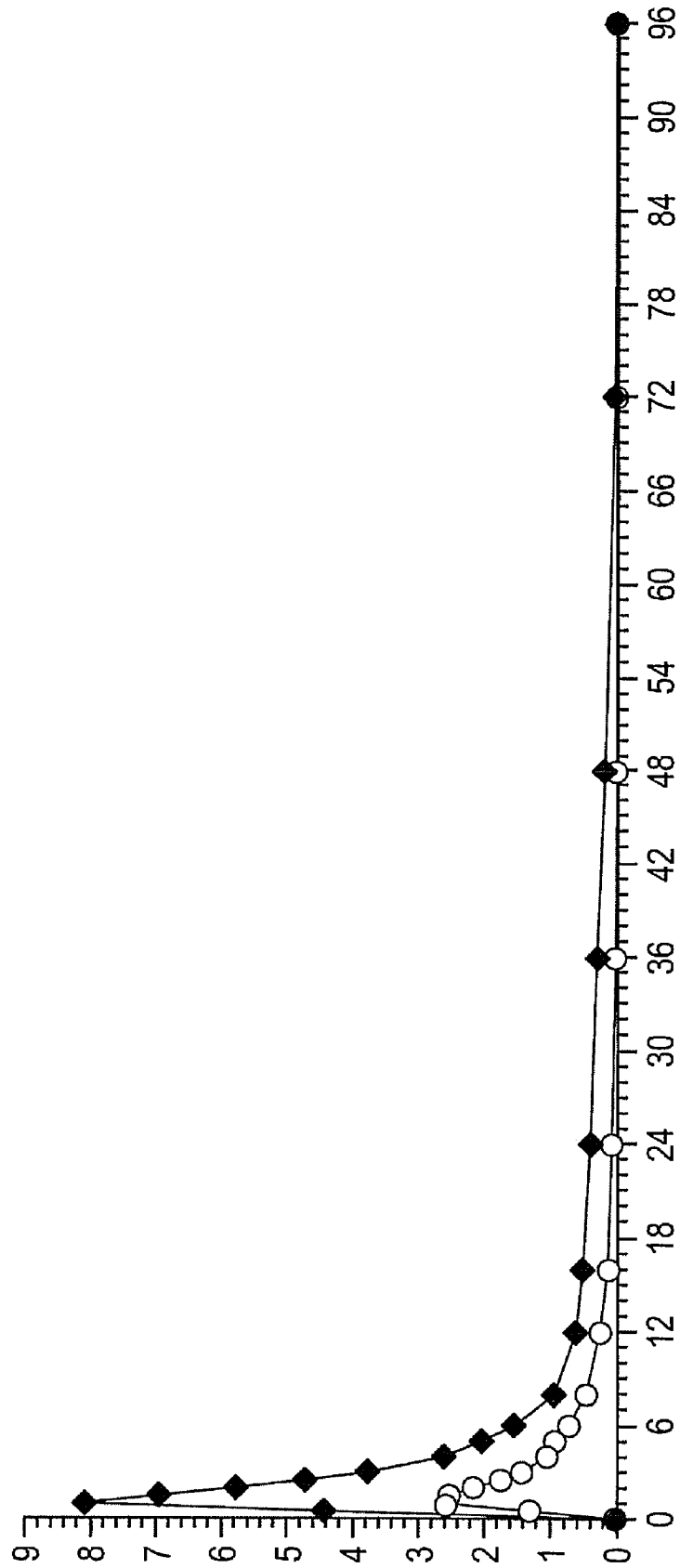
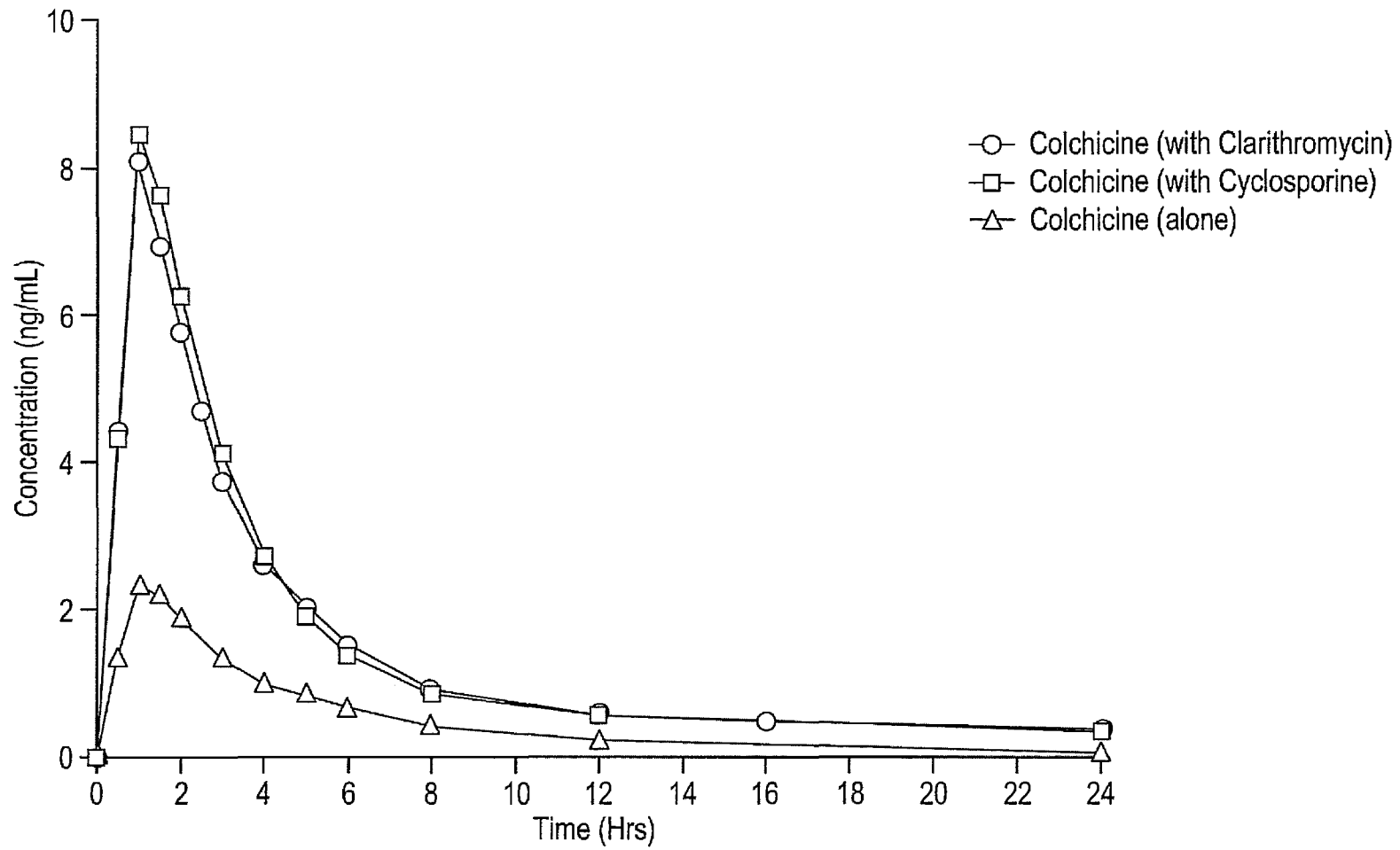


FIG. 3



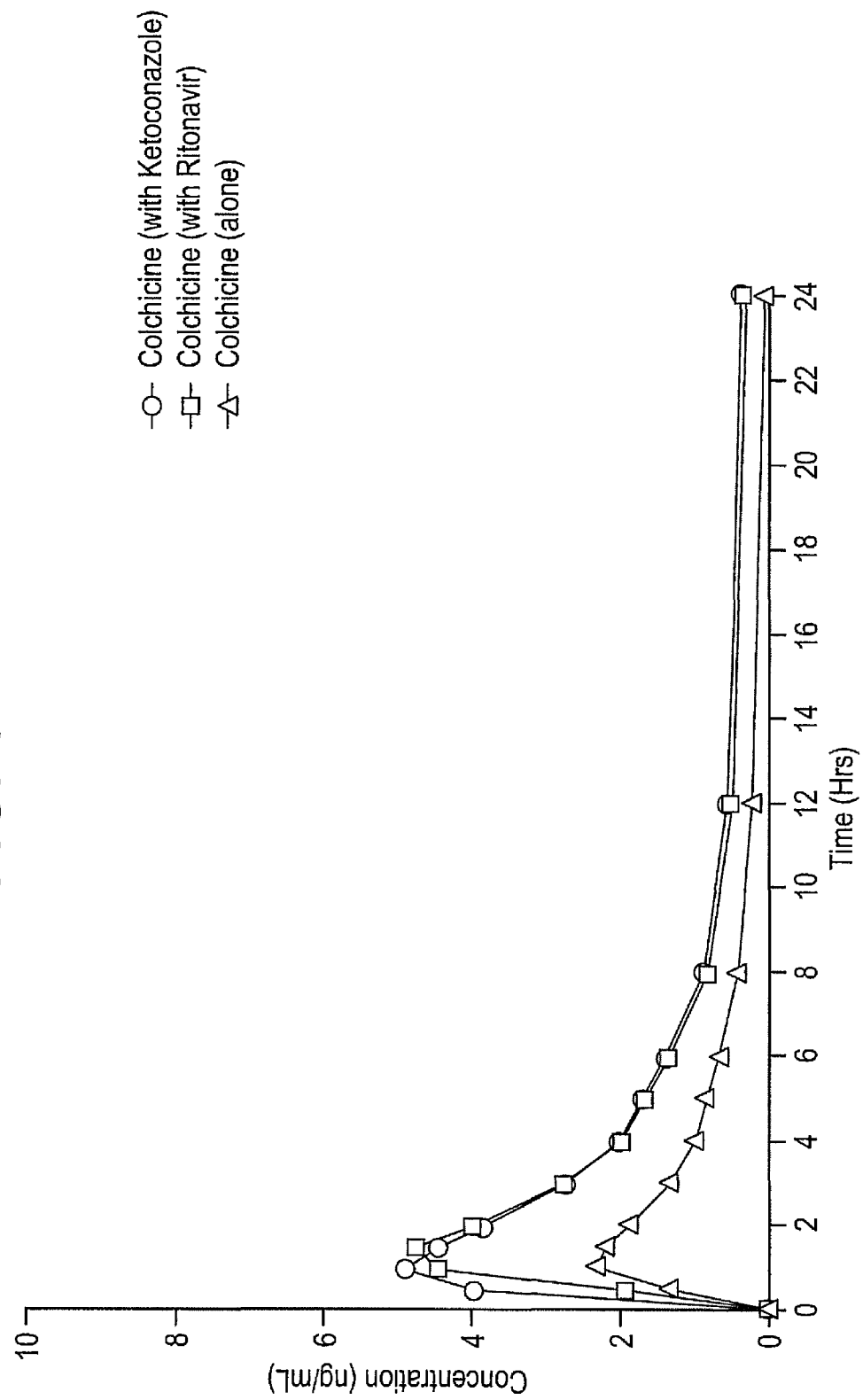
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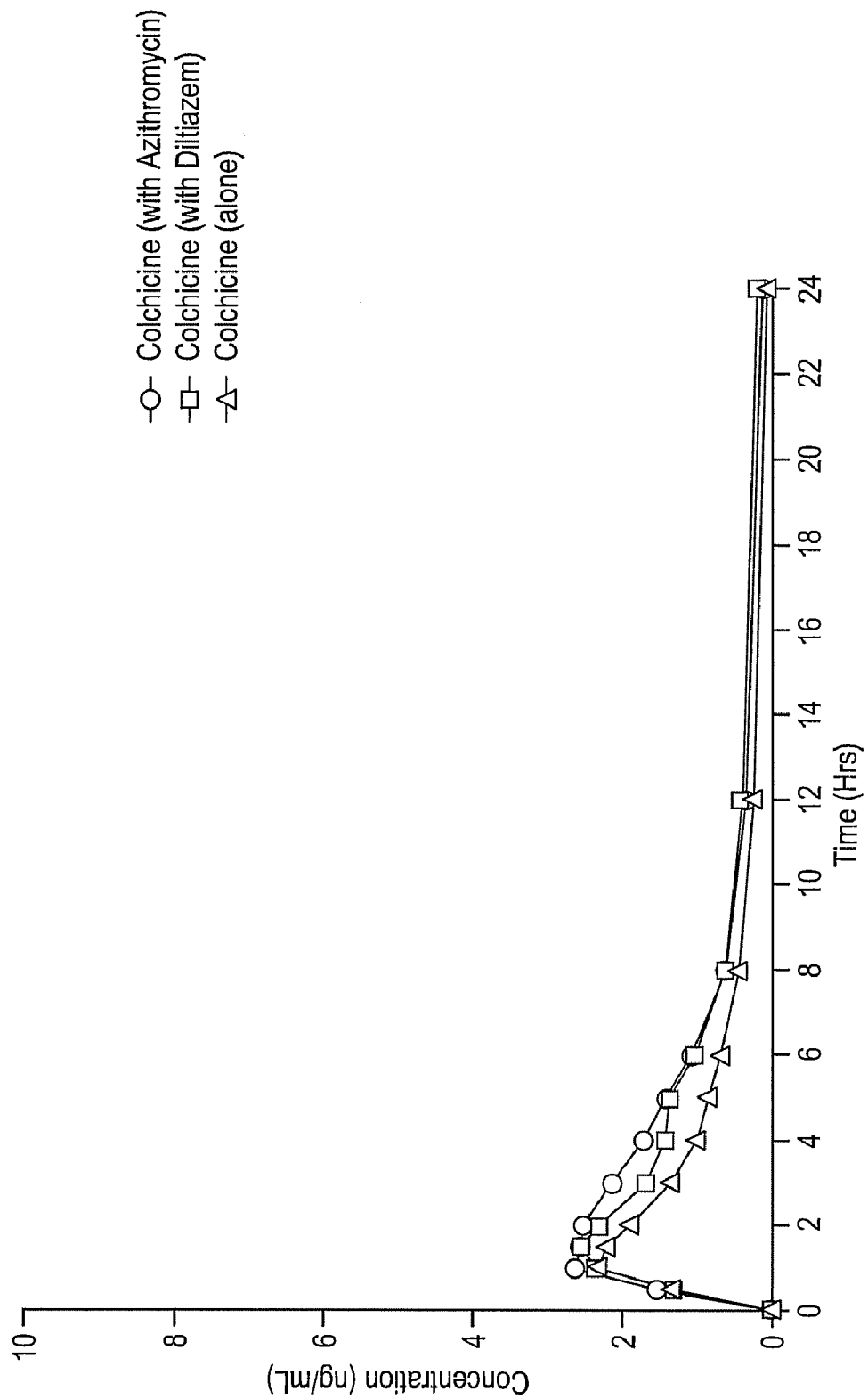
FIG. 4



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**US 7,964,648 B2****FIG. 5**

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# **METHODS FOR CONCOMITANT ADMINISTRATION OF COLCHICINE AND A SECOND ACTIVE AGENT**

## **CROSS REFERENCE TO RELATED APPLICATIONS**

This application is a Continuation of U.S. patent application Ser. No. 12/372,046, filed Feb. 17, 2009, which is a Nonprovisional of U.S. Provisional Application Ser. Nos. 61/138,141 filed Dec. 17, 2008 and 61/152,067 filed Feb. 12, 2009, all of which are hereby incorporated by reference in their entirety.

## **FIELD OF THE DISCLOSURE**

This disclosure relates to methods allowing for the co-administration of colchicine together with one or more second active agents for therapeutic purposes with improved safety compared to prior methods of administration.

## **BACKGROUND**

Colchicine, chemical name (–)-N-[(7S, 12aS)-1,2,3,10-tetramethoxy-9-oxo-5,6,7,9-tetrahydrobenzo[a]heptalen-7-yl]-acetamide, is an alkaloid found in extracts of *Colchicum autumnale*, *Gloriosa superba*, and other plants. It is a microtubule-disrupting agent used in the treatment of gout and other conditions that may be treated, relieved or prevented with anti-inflammatory treatment. Colchicine impairs the motility of granulocytes and can prevent the inflammatory phenomena that initiate an attack (or flare) of gout. Colchicine also inhibits mitosis, resulting in effects in cells with high turnover rates such as those in the gastrointestinal tract and bone marrow. The primary adverse side effects of colchicine therapy include gastrointestinal upset such as diarrhea and nausea.

Colchicine has a narrow therapeutic index. The margin between an effective dose and a toxic dose of colchicine is much narrower than that of many other widely used drugs. Consequently, actions that result in increased colchicine levels in patients receiving colchicine therapy are particularly dangerous. Co-administration of colchicine to patients along with certain other drugs can have the effect of increasing colchicine levels. Such drug-drug interactions with colchicine have been reported to result in serious morbid complications and, in some cases, death.

Colchicine is rapidly absorbed from the gastrointestinal tract. Peak concentrations occur in 0.5 to 2 hours. The drug and its metabolites are distributed in leukocytes, kidneys, liver, spleen and the intestinal tract. Colchicine is metabolized in the liver and excreted primarily in the feces with 10 to 20% eliminated unchanged in the urine.

Gout (or gouty arthritis) is a disease caused by a build up of uric acid in the joints. Such a build up is typically due to an overproduction of uric acid, or to a reduced ability of the kidney to excrete uric acid. Gout is characterized by excruciating, sudden, unexpected, burning pain, as well as by swelling, redness, warmth, and stiffness in the affected joint. Low-grade fever may also be present. A gout flare is a sudden attack of pain in affected joints, especially in the lower extremities, and most commonly in the big toe. In afflicted individuals, the frequency of gout flares typically increases over time. In this manner, gout progresses from acute gout to chronic gout, which involves repeated episodes of joint pain.

Colchicine can reduce pain in attacks of acute gout flares and also can be used beneficially for treating adults for pro-

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phylaxis of gout flares. Although its exact mode of action in the relief of gout is not completely understood, colchicine is known to decrease the inflammatory response to urate crystal deposition by inhibiting migration of leukocytes, to interfere with urate deposition by decreasing lactic acid production by leukocytes, to interfere with kinin formation and to diminish phagocytosis and subsequent inflammatory responses.

Cytochrome p450 (CYP) enzymes are agents of drug metabolism that are found in the liver, the gastrointestinal tract and other locations in the body. CYP enzymes occur in a variety of closely related proteins referred to as isozymes and different CYP isozymes may preferentially metabolize different drugs. The 3A family of CYP isozymes, particularly CYP3A4, is also known to be involved in many clinically significant drug-drug interactions, including those involving colchicine and second active agents. While drugs are often targets of CYP-mediated metabolism, some may also alter the expression and activity of such enzymes, thus impacting the metabolism of other drugs. The biotransformation of colchicine in human liver microsomes involves formation of 3-demethylcolchicine and 2-demethylcolchicine. As shown by experiments using antibodies against CYP3A4 and experiments using chemical inhibition of CYP3A4, this transformation is correlated with (and thus apparently mediated by) CYP3A4 activity.

P-glycoprotein (P-gp) is an ATP-dependent cell surface transporter molecule that acts as an ATPase efflux pump for multiple cytotoxic agents, including colchicine. P-gp actively pumps certain compounds, including drugs such as colchicine, out of cells. P-gp is encoded by the Adenosine triphosphate-binding cassette subfamily B member 1 (ABCB1) gene, also referred to as the multiple drug resistance 1 gene (MDR1).

Since colchicine acts intracellularly, the combined effects of CYP3A4 inhibition and P-gp inhibition by second active agents that also interact with CYP3A4 and P-gp can cause colchicine toxicity in patients taking what would be a safe dose of colchicine in the absence of concomitant second agent administration. Various studies of adverse reactions from exposure to multiple drugs have found that 6.5-23% of the adverse reactions result from drug-drug interactions. Unfortunately, each year a number of deaths occur as the direct result of patients adding a concomitant prescription pharmaceutical product to their existing medication regimen.

There accordingly remains a need for improved methods for administering colchicine to individuals who are concomitantly being treated with second active agents so as to reduce the possibility of colchicine toxicity while maintaining the sometimes life-saving advantages of being able to administer the two (or more) agents concomitantly. The present disclosure addresses this need and provides further advantages.

## **SUMMARY**

In one embodiment, a method of treating an individual in need of treatment with colchicine comprises concomitantly administering to the individual colchicine and another drug, for example, ketoconazole or ritonavir or cyclosporine, wherein the colchicine is administered as a dosing regimen with a starting colchicine dose of no more than about 0.6 mg colchicine, followed by either: no additional colchicine doses within about 12, 24, 48, or 72 hours, or at least one additional colchicine dose within about 12 hours and no more frequently than once every hour wherein each additional colchicine dose is no greater than about 0.6 mg. According to another embodiment, the other drug is, for example, verapamil or diltiazem, and the starting colchicine dose during coadministration with

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the other drug is no more than about 1.2 mg colchicine, followed by either: no additional colchicine doses within about 12, 24, 48, or 72 hours, or at least one additional colchicine dose within about 12 hours.

In another aspect, a method of using colchicine comprises increasing the blood plasma levels of colchicine in a individual being administered doses of about 0.6 mg or less of colchicine to treat a colchicine-treatable condition, said method comprising the concomitant dosing of the individual with a sufficient amount of ketoconazole to increase the  $C_{max}$  of colchicine by about 90%, or to increase the  $AUC_{0-t}$  of colchicine in the individual by about 190%, or to increase the  $AUC_{0-inf}$  of colchicine in the individual by about 205%, or to decrease the clearance of colchicine by about 70%, compared to the  $C_{max}$ ,  $AUC_{0-t}$ ,  $AUC_{0-inf}$  or clearance in a matched individual not administered concomitant ketoconazole.

In yet another aspect, a method of using colchicine comprises increasing the blood plasma levels of colchicine in an individual being administered doses of about 0.6 mg or less of colchicine to treat a colchicine-treatable condition, said method comprising the concomitant dosing of the individual with a sufficient amount of ritonavir to increase the  $C_{max}$  of colchicine by about 170%, or to increase the  $AUC_{0-t}$  of colchicine in the individual by about 245%, or to decrease the clearance of colchicine by about 70%, compared to the  $C_{max}$ ,  $AUC_{0-t}$ , or clearance in a matched individual not administered concomitant ritonavir.

In another embodiment, a method for using colchicine comprises a pharmacy receiving a prescription for colchicine for a patient who is concomitantly being treated with ketoconazole or ritonavir or verapamil, and the pharmacy dispensing colchicine in response to receipt of the prescription, wherein the dispensing is preceded by: entering, into a first computer readable storage medium in functional communication with a computer, of a unique patient identifier for said patient and at least one drug identifier for colchicine linked to the patient identifier so as to indicate that colchicine is to be administered to the patient, wherein the computer has been programmed to issue a drug-drug interaction alert when the at least one drug identifier for colchicine is entered linked to the patient identifier so as to indicate that colchicine is to be administered to the patient and when the patient identifier is also linked to an identifier indicating that ketoconazole or ritonavir or verapamil is being concomitantly administered to the patient, wherein, upon entry of the at least one drug identifier for colchicine linked to the patient identifier, a drug-drug interaction alert is issued to one or more of a pharmacy technician, a pharmacist, or a pharmacy customer obtaining the colchicine, said alert indicating that that ketoconazole or ritonavir is being concomitantly administered to the patient and that prior to the colchicine being dispensed, the colchicine dosing regimen must be reviewed and, if necessary adjusted, so that when the colchicine is delivered to the pharmacy customer obtaining the colchicine it is delivered along with instructions for the colchicine to be taken in accordance with a dosing regimen of no more than about 0.6 mg colchicine, followed by either: no additional colchicine doses within about 12, 24, 48, or 72 hours, or at least one additional colchicine dose within about 12 hours and no more frequently than once every hour wherein each additional colchicine dose is no greater than about 0.6 mg.

A method of treating a patient with colchicine comprises administering an adjusted daily dosage amount of colchicine to the patient who is receiving concomitant administration of ritonavir, wherein the adjusted daily dosage amount of colchicine is about 25% to 50% of an intended daily dosage amount of colchicine, and wherein the intended daily dosage amount

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of colchicine is a dose suitable for the patient if the patient were not receiving concomitant ritonavir.

A method of treating a patient with colchicine comprises administering an adjusted daily dosage amount of colchicine to the patient who is receiving concomitant administration of ketoconazole, wherein the adjusted daily dosage amount of colchicine is about 25% to 50% of an intended daily dosage amount of colchicine, and wherein the intended daily dosage amount of colchicine is a daily dosage amount suitable for the patient if the patient were not receiving concomitant ketoconazole.

A method of treating an individual in need of treatment for gout flares, comprises concomitantly administering colchicine and azithromycin, and carefully monitoring the individual for potential toxicity. The method further comprises adjusting the dose of colchicine or azithromycin as necessary to avoid adverse side effects.

A method of treating an individual with colchicine comprises concomitantly administering colchicine and verapamil, and carefully monitoring the individual for signs and symptoms of adverse side effects. The method further comprises administering an adjusted daily dosage amount of colchicine to the patient who is receiving concomitant administration of verapamil, wherein the adjusted daily dosage amount of colchicine is about 50% to 75% of an intended daily dosage amount of colchicine, and wherein the intended daily dosage amount of colchicine is a daily dosage amount suitable for a patient if the patient were not receiving concomitant verapamil.

## BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows mean colchicine plasma concentrations following administration of single and multiple oral doses of colchicine 0.6 mg in healthy adults, N=13, Y axis=colchicine concentration, ng/mL, X axis=time in hours, ◆=day 1, ■=day 25. See Example 1.

FIG. 2 shows a pharmacokinetic profile comparison of single-dose colchicine (0.6 mg, alone) and single-dose colchicine (0.6 mg) co-administered with steady-state clarithromycin in healthy adults, Y axis=colchicine concentration, ng/mL, X axis=time in hours, N=23, ●=colchicine alone, ◆=colchicine plus clarithromycin. See Example 2.

FIG. 3 shows a pharmacokinetic profile comparison of single-dose colchicine (0.6 mg, alone) and single-dose colchicine (0.6 mg) co-administered with steady-state clarithromycin and steady-state cyclosporine in healthy adults. Y axis=colchicine concentration, ng/mL, X axis=time in hours, N=18, ▲=colchicine alone, ●=colchicine plus clarithromycin, ■=colchicine plus cyclosporine.

FIG. 4 shows a pharmacokinetic profile comparison of single-dose colchicine (0.6 mg, alone) and single-dose colchicine (0.6 mg) co-administered with steady-state ketoconazole and steady-state ritonavir in healthy adults. Y axis=colchicine concentration, ng/mL, X axis=time in hours, N=18, ▲=colchicine alone, ●=colchicine plus ketoconazole, ■=colchicine plus ritonavir.

FIG. 5 shows a pharmacokinetic profile comparison of single-dose colchicine (0.6 mg, alone) and single-dose colchicine (0.6 mg) co-administered with steady-state azithromycin and steady-state diltiazem in healthy adults. Y axis=colchicine concentration, ng/mL, X axis=time in hours, N=18, ▲=colchicine alone, ●=colchicine plus azithromycin, ■=colchicine plus diltiazem.

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These and other embodiments, advantages and features of the present invention become clear when detailed description is provided in subsequent sections.

## DETAILED DESCRIPTION

Disclosed herein are methods for safely administering colchicine concomitantly with a second active agent, wherein the second active agent is a CYP3A4 inhibitor, a P-gp inhibitor, or both. Exemplary second active agents that are CYP3A4 and P-gp inhibitors are azithromycin, ketoconazole, ritonavir, diltiazem, verapamil and cyclosporine. It has now been discovered that certain reduced or limited colchicine dosage amounts, when administered with concomitantly administered recommended dosage amounts of second active agents that are CYP3A4 inhibitors, P-gp inhibitors, or both, achieve plasma colchicine levels that are therapeutically effective, but are not significantly higher, and therefore not significantly more toxic, than plasma levels achieved by administration of manufacturers' recommended colchicine dosages in the absence of concomitant administration with the second active agent. Thus, colchicine and second active agents that are CYP3A4 inhibitors, P-gp inhibitors, or both, can be administered concomitantly with improved safety when colchicine is administered as disclosed herein.

Without being held to theory, it has been hypothesized by the inventors herein that P-gp inhibition is more important in the elimination of colchicine than CYP3A4 inhibition. The CYP3A4 and P-gp inhibition potential of clarithromycin, azithromycin, ketoconazole, ritonavir, diltiazem and cyclosporine are given in Table 1. Based on their level of P-gp inhibition, it was predicted that clarithromycin and cyclosporine will increase colchicine concentrations more than ketoconazole or ritonavir, which will increase colchicine levels more than verapamil, azithromycin or diltiazem. The results presented herein confirm this hypothesis.

TABLE 1

CYP3A4 and P-gp inhibition potential of second active agents		
Drug	CYP3A Inhibition potential	P-gp Inhibition potential
Clarithromycin	+++++	+++++
Cyclosporine	+++++	+++++
Ketoconazole	+++++	+++
Ritonavir	+++++	+++
Verapamil	++	++
Diltiazem	+	+
Azithromycin	+	+

Ritonavir (Norvir®, Abbott Laboratories) is an inhibitor of Human Immunodeficiency Virus (HIV) protease and is approved for the treatment of HIV-infection when used as part of a highly active antiretroviral therapy (HAART) regimen at the recommended dose of 600 mg twice daily. Although a very potent and effective protease inhibitor at the recommended dose, ritonavir is not well tolerated by HIV-infected patients at the approved dose and therefore, is generally not used clinically as a sole, therapeutic protease inhibitor within a HAART regimen. Rather, ritonavir is used more often as a pharmacokinetic enhancer or 'boosting agent' when combined with other approved protease inhibitors that are CYP3A4 and P-gp substrates and also have inherent bioavailability issues, such as poor bioavailability due to first pass effect. Improving the pharmacokinetic disposition of other protease inhibitors is possible due to the potent CYP3A4 and P-gp inhibitory activity ritonavir possesses. Sub-therapeutic ritonavir doses are used to achieve pharmacokinetic enhance-

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ment of the co-administered protease inhibitors; typically 100 mg of ritonavir administered twice daily is the ritonavir dose used in combination with the primary protease inhibitor. This low-dose ritonavir regimen boosts the bioavailability of the second protease inhibitor without contributing significantly to the adverse event profile of the HAART regimen.

Cyclosporine (Neoral®, Novartis Pharmaceuticals Corporation) is the active principle in Neoral® an oral formulation that immediately forms a microemulsion in an aqueous environment. Cyclosporine is indicated for kidney, liver, and heart transplantation; rheumatoid arthritis and psoriasis. Cyclosporine is extensively metabolized by the CYP3A4 enzyme system in the liver, and to a lesser degree in the gastrointestinal tract, and the kidney. The metabolism of cyclosporine can be altered by the co-administration of a variety of agents.

Ketoconazole is a synthetic broad-spectrum antifungal agent available in scored white tablets, each containing 200 mg ketoconazole base for oral administration. Ketoconazole tablets are indicated for the treatment of the following systemic fungal infections: candidiasis, chronic mucocutaneous candidiasis, oral thrush, candiduria, blastomycosis, coccidioidomycosis, histoplasmosis, chromomycosis, and paracoccidioidomycosis. Ketoconazole is a potent inhibitor of the CYP3A4 enzyme system. Co-administration of ketoconazole and drugs primarily metabolized by the CYP3A4 enzyme may result in increased plasma concentrations of the drugs that could increase or prolong both therapeutic and adverse side effects.

Azithromycin is a macrolide antibiotic indicated for the treatment of patients with mild to moderate infections caused by susceptible strains of the designated microorganisms in specific conditions. Azithromycin remains the sole agent developed and marketed within the azalide macrolide subclass. Due to its dibasic structure, azithromycin has demonstrated unique pharmacokinetic properties that differ significantly from those of classic macrolide agents. Azithromycin's pharmacokinetics are characterized by low concentrations in serum, secondary to rapid and significant uptake by fibroblasts and acute reactant cells such as polymorphonuclear leukocytes (PMNs), monocytes, and lymphocytes. Azithromycin is a weak to moderate CYP3A4 inhibitor.

Diltiazem (Cardizem® CD, Biovail Pharmaceuticals, Inc. [Biovail]) is an extended-release (ER) calcium ion influx inhibitor available in blue capsules, each containing 240 mg diltiazem hydrochloride for oral administration. Diltiazem ER capsules are indicated for the treatment of hypertension and the management of chronic stable angina and angina due to coronary artery spasm. Diltiazem is a CYP3A4 and P-gp inhibitor.

Verapamil HCl ER (Mylan Pharmaceuticals, Inc.) is a calcium ion influx inhibitor available in a pale green, capsule shaped, film-coated tablets, each containing 240 mg verapamil hydrochloride for oral administration. Verapamil HCl ER tablets are indicated for the management of hypertension. Verapamil HCl ER is a potent CYP3A4 and P-gp inhibitor.

In one embodiment, colchicine is administered to an individual suffering from a condition treatable with colchicine, and the concomitant second active agent (e.g., ketoconazole, ritonavir, cyclosporine, verapamil, or diltiazem or any other CYP3A4 or P-gp inhibitor) is administered concurrently while the colchicine administration is reduced, or the individual has recently completed a dosing regimen of the second active agent, in which case the colchicine administration may still be reduced for a period of time.

In one embodiment, disclosed herein is a method of administering colchicine and a second active agent (e.g., ketoconazole).

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zole, ritonavir, or cyclosporine) wherein an individual is administered the colchicine according to a colchicine dosing regimen of a single starting colchicine dose of no more than about 0.6 mg colchicine, followed by either no additional colchicine doses within about 12, 24, 48, or 72 hours, or followed by at least one additional colchicine dose within 12 hours and no more frequently than once every hour (e.g., every 3, 4, 6, 8, or 12 hours). In this embodiment, each additional colchicine dose is specifically no greater than about 0.3 mg and the individual is an adult individual or a pediatric individual. Specifically, the starting colchicine dose is about 0.6 mg or about 0.3 mg, and each additional colchicine dose is about 0.3 mg. In one embodiment, when additional doses are administered, only two, three, or four additional colchicine doses are administered within about 24 hours. Specifically, the individual is an adult individual and the starting colchicine dose is about 0.6 mg, and each additional colchicine dose, if any, is about 0.3 mg. In one embodiment, only three additional colchicine doses are administered within about 24 hours.

In one embodiment, disclosed herein is a method of administering colchicine and a second active agent (e.g., verapamil or diltiazem) wherein an individual is administered the colchicine according to a colchicine dosing regimen of a single starting colchicine dose of no more than about 1.2 mg colchicine, followed by either no additional colchicine doses within about 12, 24, 48, or 72 hours, or followed by at least one additional colchicine dose within 12 hours and no more frequently than once every hour (e.g., every 3, 4, 6, 8, or 12 hours). In this embodiment, each additional colchicine dose is specifically no greater than about 0.3 mg or 0.6mg and the individual is an adult individual or a pediatric individual. Specifically, the starting colchicine dose is about 0.6mg or 1.2 mg, and each additional colchicine dose is about 0.3 mg or 0.6mg. In one embodiment, when additional doses are administered, only two, three, or four additional colchicine doses are administered within about 24 hours. Specifically, the individual is an adult individual and the starting colchicine dose is about 1.2 mg, and each additional colchicine dose, if any, is about 0.3 mg or 0.6 mg. In one embodiment, only three additional colchicine doses are administered within about 24 hours.

In one embodiment, the second active agent is ketoconazole or ritonavir. In one embodiment, the ketoconazole is administered to the individual at a dosage of about 200 mg daily and the colchicine dosing regimen is one about 0.6 mg colchicine dose to start, followed by 0, 1, 2, 3, or 4 additional colchicine doses of about 0.6 mg every 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 hours (e.g., every 2, 3, 4, 5, or 6 hours) after the preceding colchicine dose. In another embodiment, the ritonavir is administered to the individual at a dosage of about 200 to 1200 mg daily (e.g., in 2x100 mg doses or 2x600 mg doses) and the colchicine dosing regimen is one about 0.6 mg colchicine dose to start, followed by 0, 1, 2, 3, or 4 additional colchicine doses of about 0.6 mg every 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 hours (e.g., every 2, 3, 4, 5, or 6 hours) after the preceding colchicine dose. In an exemplary regimen for treatment of acute gout flares, ingestion of colchicine is continued until a total of no more than about 1.2, 1.4, 1.6, 1.8, 2, or 2.4 mg of colchicine has been ingested, after which ingestion of colchicine is stopped until a subsequent acute gout flare occurs. More preferably, the colchicine is administered as a dosage form of 0.6 mg (e.g., one 0.6 mg colchicine tablet), or 0.3 mg (e.g., one half of a 0.6 mg tablet) of colchicine and administration of the dosage form is not repeated within a period of at least about two days, preferably at least about three days.

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In one embodiment, the second active agent (e.g., ketoconazole or ritonavir or cyclosporine) is administered to the individual before the colchicine is administered to the individual, and wherein the administration of second active agent is terminated no more than about fourteen days prior to the initiation of colchicine administration. For example, the method comprises administering colchicine to an individual also taking a second active agent (e.g., ketoconazole or ritonavir or cyclosporine), or having completed treatment with the second active agent within the prior 14 days, the individual being administered a single dose of about 0.6 mg or about 0.3 mg of colchicine to treat a gout flare, which administration is not repeated within any 3-day period. According to this embodiment if the second active agent is instead verapamil or diltiazem, if the second active agent is terminated no more than about fourteen days prior to the initiation of the colchicine administration to treat a gout flare, the single dose of colchicine is about 1.2mg not to be repeated within a 3-day period.

In another aspect, herein disclosed is a method for increasing the blood plasma levels of colchicine in an individual to whom colchicine is being administered to treat or prevent a colchicine-responsive condition. This method comprises the concomitant dosing of the individual with a sufficient amount of ketoconazole to increase the  $C_{max}$  of colchicine by about 90%, or to increase the  $AUC_{0-t}$  of colchicine in the individual by about 190%, or to increase the  $AUC_{0-inf}$  of colchicine in the individual by about 205%, or to decrease the clearance of colchicine by about 70%, compared to the  $C_{max}$ ,  $AUC_{0-t}$ , or clearance in the same or a matched individual when not being administered a concomitant ketoconazole. In a specific embodiment, the individual is being administered no more than hourly doses of about 0.6 mg of colchicine or less, and the amount of ketoconazole is about 200 mg. In one embodiment, the single dose is one 0.6 mg colchicine tablet.

In yet another aspect, herein disclosed is a method for increasing the blood plasma levels of colchicine in an individual to whom colchicine is being administered to treat or prevent a colchicine-responsive condition. This method comprises the concomitant dosing of the individual with a sufficient amount of ritonavir to increase the  $C_{max}$  of colchicine by about 170%, or to increase the  $AUC_{0-t}$  of colchicine in the individual by about 245%, or to decrease the clearance of colchicine by about 70%, compared to the  $C_{max}$ ,  $AUC_{0-t}$ , or clearance in the same or a matched individual when not being administered concomitant ritonavir. In a specific embodiment, the individual is being administered no more than hourly doses of about 0.6 mg of colchicine or less, and the amount of ritonavir is about 200 to about 1200 mg. In one embodiment, the single dose is one 0.6 mg colchicine tablet.

In one embodiment, a method of treating a patient with colchicine comprises administering an adjusted daily dosage amount of colchicine to the patient who is receiving concomitant administration of ritonavir, wherein the adjusted daily dosage amount of colchicine is 25% to 50% of an intended daily dosage amount of colchicine, and wherein the intended daily dosage amount of colchicine is a daily dosage amount suitable for the patient if the patient were not receiving concomitant ritonavir. Treating is, for example, to prevent gout flares, to treat acute gout, or to treat familial Mediterranean fever. When the colchicine is administered to prevent gout flares, the adjusted daily dosage amount of colchicine may be reduced from a 0.6 mg twice daily intended dose to a 0.6 mg once daily adjusted dose. Alternatively, when the colchicine is administered to prevent gout flares, wherein the adjusted daily dosage amount of colchicine is reduced from a 0.6 mg once daily intended dose to a 0.3 mg once daily adjusted dose.

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In one embodiment, when treating is for acute gout, the intended daily dosage amount is 1.8 to 2.4 mg, and the maximum adjusted daily dosage amount is 0.6 mg, not to be repeated within 3 days. In another embodiment, treating is for acute gout, the intended daily dosage amount is 2.4 to 4.8 mg and the maximum adjusted daily dosage amount is 0.6 to 1.2 mg, not to be repeated within 3 days. In yet another embodiment, treating is for familial Mediterranean fever and the daily dosage amount 1.2 to 2.4 mg for adults, and the maximum adjusted daily dosage amount is 0.6 mg, given, for example, in two 0.3 mg doses. In another embodiment, treating is for familial Mediterranean fever and the intended daily dosage amount is 0.9 to 1.8 mg for children 6-12 years or 4-6 years, and the maximum adjusted daily dosage amount is 0.6 mg, given, for example, in two 0.3 mg doses. The concomitantly administered dose of ritonavir is, for example, 200 mg per day. In one embodiment, the ritonavir is administered to the patient before the colchicine is administered to the patient, and wherein the administration of ritonavir is terminated no more than about fourteen days prior to the initiation of colchicine administration. The method optionally further comprises carefully monitoring the individual for potential toxicity. Any 0.3 mg dose contemplated in this method can be a single 0.3 mg dosage form or one-half a 0.6 mg dosage form, e.g. one-half a 0.6 mg colchicine tablet.

A method of treating a patient with colchicine comprises administering an adjusted daily dosage amount of colchicine to the patient who is receiving concomitant administration of ketoconazole, wherein the adjusted daily dosage amount of colchicine is 25% to 50% of an intended daily dosage amount of colchicine, and wherein the intended daily dosage amount of colchicine is a daily dosage amount suitable for the patient if the patient were not receiving concomitant ketoconazole. Treating is, for example, to prevent gout flares, to treat acute gout, or to treat familial Mediterranean fever. When the colchicine is administered to prevent gout flares, the adjusted daily dosage amount of colchicine may reduced from a 0.6 mg twice daily intended dose to a 0.6 mg once daily adjusted dose. Alternatively, when the colchicine is administered to prevent gout flares, wherein the adjusted daily dosage amount of colchicine is reduced from a 0.6 mg once daily intended dose to a 0.3 mg once daily adjusted dose. In one embodiment, when treating is for acute gout, the intended daily dosage amount is 1.8 to 2.4 mg, and the maximum adjusted daily dosage amount is 0.6 mg, not to be repeated within 3 days. In another embodiment, treating is for acute gout, the intended daily dosage amount is 2.4 to 4.8 mg and the maximum adjusted daily dosage amount is 0.6 to 1.2 mg, not to be repeated within 3 days. In yet another embodiment, treating is for familial Mediterranean fever and the daily dosage amount 1.2 to 2.4 mg for adults, and the maximum adjusted daily dosage amount is 0.6 mg, given, for example, in two 0.3 mg doses. In another embodiment, treating is for familial Mediterranean fever and the intended daily dosage amount is 0.9 to 1.8 mg for children 6-12 years or 4-6 years, and the maximum adjusted daily dosage amount is 0.6 mg, given, for example, in two 0.3 mg doses. The concomitantly administered dose of ketoconazole is, for example, 250 mg per day. In one embodiment, the ketoconazole is administered to the patient before the colchicine is administered to the patient, and wherein the administration of ketoconazole is terminated no more than about fourteen days prior to the initiation of colchicine administration. The method optionally further comprises carefully monitoring the individual for potential toxicity. Any 0.3 mg dose contemplated in this method can be a single 0.3 mg dosage form or one-half a 0.6 mg dosage form, e.g. one-half a 0.6 mg colchicine tablet.

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A method of treating a patient with colchicine comprises administering an adjusted daily dosage amount of colchicine to the patient who is receiving concomitant administration of cyclosporine, wherein the adjusted daily dosage amount of colchicine is 25% to 50% of an intended daily dosage amount of colchicine, and wherein the intended daily dosage amount of colchicine is a daily dosage amount suitable for the patient if the patient were not receiving concomitant cyclosporine. Treating is, for example, to prevent gout flares, to treat acute gout, or to treat familial Mediterranean fever. When the colchicine is administered to prevent gout flares, the adjusted daily dosage amount of colchicine may reduced from a 0.6 mg twice daily intended dose to a 0.3 mg once daily adjusted dose. Alternatively, when the colchicine is administered to prevent gout flares, wherein the adjusted daily dosage amount of colchicine is reduced from a 0.6 mg once daily intended dose to a 0.3 mg once every other day adjusted dose. In one embodiment, when treating is for acute gout, the intended daily dosage amount is 1.8 to 2.4 mg, and the maximum adjusted daily dosage amount is 0.6 mg, not to be repeated within 3 days. In another embodiment, treating is for acute gout, the intended daily dosage amount is 2.4 to 4.8 mg and the maximum adjusted daily dosage amount is 0.6 to 1.2 mg, not to be repeated within 3 days. In yet another embodiment, treating is for familial Mediterranean fever and the daily dosage amount 1.2 to 2.4 mg for adults, and the maximum adjusted daily dosage amount is 0.6 mg, given, for example, in two 0.3 mg doses. In another embodiment, treating is for familial Mediterranean fever and the intended daily dosage amount is 0.9 to 1.8 mg for children 6-12 years or 4-6 years, and the maximum adjusted daily dosage amount is 0.6 mg, given, for example, in two 0.3 mg doses. The concomitantly administered dose of cyclosporine can be various dosage strengths administered per day, and can be administered as an oral preparation, topically, or intravenously. In one embodiment, the cyclosporine is administered to the patient before the colchicine is administered to the patient, and wherein the administration of cyclosporine is terminated no more than about fourteen days prior to the initiation of colchicine administration. The method optionally further comprises carefully monitoring the individual for potential toxicity. Any 0.3 mg dose contemplated in this method can be a single 0.3 mg dosage form or one-half a 0.6 mg dosage form, e.g. one-half a 0.6 mg colchicine tablet.

In another embodiment, colchicine is concomitantly administered with azithromycin. Concomitant administration of azithromycin with colchicine increases exposure to colchicine approximately 46% and thus has the potential to produce colchicine toxicity. During concomitant use of azithromycin and colchicine, the physician should carefully monitor individuals for any signs or symptoms of colchicine toxicity. Additionally, dosing adjustments to either the colchicine and/or the azithromycin may be necessary to avoid adverse side effects.

A method of treating a patient with colchicine comprises administering an adjusted daily dosage amount of colchicine to the patient who is receiving concomitant administration of verapamil, wherein the adjusted daily dosage amount of colchicine is 50% to 75% of an intended daily dosage amount of colchicine, and wherein the intended daily dosage amount of colchicine is a daily dosage amount suitable for the patient if the patient were not receiving concomitant verapamil. Treating is, for example, to prevent gout flares, to treat acute gout, or to treat familial Mediterranean fever. When the colchicine is administered to prevent gout flares, the adjusted daily dosage amount of colchicine may reduced from a 0.6 mg twice daily intended dose to a 0.3 mg once daily adjusted

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dose. In one embodiment, when treating is for acute gout, the intended daily dosage amount is 1.8 to 2.4 mg, and the maximum adjusted daily dosage amount is 1.2 mg. In another embodiment, treating is for acute gout, the intended daily dosage amount is 2.4 to 4.8 mg and the maximum adjusted daily dosage amount is about one-third the intended daily dosage amount. In yet another embodiment, treating is for familial Mediterranean fever and the daily dosage amount 1.2 to 2.4 mg for adults, and the maximum adjusted daily dosage amount is 1.2 mg, given, for example, in two 0.6 mg doses. In one embodiment, the verapamil is administered to the patient

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## Acute Gout

Acute gout, or gout flares, can be treated according to the following treatment schedule. This table indicates the original, or intended, dose, i.e., the dose of colchicine recommended absent concomitant administration of the drugs listed below. This table also presents the dose adjustment of the present invention, or the recommended colchicine dose to be administered when the strong and moderate CYP3A4 and P-gp inhibitors are administered concomitantly with colchicine when the patient is being treated for acute gout, or an acute gout flare.

Drug	Colchicine Dose Recommendation	
	Original Intended Dose (Total Dose)	Dose Adjustment
Strong CYP3A4 Inhibitors		
Regimen Reduced by Two Thirds		
Erythromycin	1.2 mg (2 tablets) at the first sign of the flare followed by 0.6 mg (1 tablet) one hour later.	0.6 mg (1 tablet) × 1 dose. Dose to be repeated no earlier than 3 days.
Ketoconazole		
Ritonavir	Dose to be repeated no earlier than 3 days.	
Moderate CYP3A4 Inhibitors		
Regimen Reduced by One Third		
Diltiazem	1.2 mg (2 tablets) at the first sign of the flare followed by 0.6 mg (1 tablet) one hour later.	1.2 mg (2 tablets) × 1 dose. Dose to be repeated no earlier than 3 days.
Verapamil	Dose to be repeated no earlier than 3 days.	
Strong P-gp Inhibitors		
Regimen Reduced by Two Thirds		
Cyclosporine	1.2 mg (2 tablets) at the first sign of the flare followed by 0.6 mg (1 tablet) one hour later.	0.6 mg (1 tablet) × 1 dose. Dose to be repeated no earlier than 3 days.
	Dose to be repeated no earlier than 3 days.	

before the colchicine is administered to the patient, and wherein the administration of verapamil is terminated no more than about fourteen days prior to the initiation of colchicine administration. The method optionally further comprises carefully monitoring the individual for potential toxicity. Any 0.3 mg dose contemplated in this method can be a single 0.3 mg dosage form or one-half a 0.6 mg dosage form, e.g. one-half a 0.6 mg colchicine tablet.

Disclosed herein are specific dosage reductions of colchicine that improve safety when colchicine is co-administered with certain active agents. The dose of colchicine recommended for administration without co-administration of certain other active agents, such as CYP3A4 or P-gp inhibitors, is referred to as an intended daily dosage amount. The reduced or modified daily dosage amount determined from the experiments presented herein is referred to as an adjusted daily dosage amount. An adjusted daily dosage amount is thus a daily dosage amount that can be safely co-administered with a second active agent as disclosed herein. A dose adjustment is thus a dose of colchicine and does not include cessation of colchicine, that is, a dose of 0 mg of colchicine.

In these and other embodiments, the colchicine-responsive condition is gout (e.g., a gout flare in a chronic gout sufferer), familial Mediterranean fever (FMF), thrombocytopenic purpura, pericarditis, scleroderma, or Behçet's disease. In some embodiments, the treatment with colchicine is either palliative or prophylactic. The gout may be acute gout, e.g. a gout flare, or chronic gout.

## Chronic Gout

For chronic gout, an original intended daily dosage amount is 1.2 mg or 6 mg. Alternatively, an intended daily dosage amount of chronic gout can be as much as 2.4 mg per day. The daily dosage amount for chronic gout can be administered at one time or dosed at intervals throughout the day, e.g. twice daily, three times daily, or four times daily.

Chronic gout, with and without a concomitant dose of another drug, can be treated according to the following treatment schedule:

## Colchicine Dose Adjustment for Co-administration with Interacting Drugs If No Alternative Available

Drug	Colchicine Dose Recommendation	
	Original Intended Dose	Dose Adjustment
Clarithromycin	0.6 mg twice daily	0.3 mg once daily
	0.6 mg once daily	0.3 mg once every other day
Cyclosporine	0.6 mg twice daily	0.3 mg once daily
	0.6 mg once daily	0.3 mg once every other day
Erythromycin	0.6 mg twice daily	0.3 mg once daily
	0.6 mg once daily	0.3 mg once every other day
Ritonavir	0.6 mg twice daily	0.6 mg once daily
	0.6 mg once daily	0.3 mg once daily

## Familial Mediterranean Fever

Familial Mediterranean Fever (FMF) can be treated according to the following intended daily dosing schedule:

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Age	Daily dosage amount	
	Usual	Maximum
Adults and children >12 years	1.2 mg	2.4 mg
Children >6 to 12 years	0.9 mg	1.8 mg
Children 4 to 6 years	0.3 mg	1.8 mg

When colchicine is given to patients with FMF concomitantly with other drugs, the adjusted (reduced) dosage amount of colchicine, according to this embodiment, is provided in the table below:

Concomitant Drug Class or Food	Noted or Anticipated Outcome	Clinical Comment
Strong CYP3A4 Inhibitors: atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin	Significant increase in colchicine plasma levels <sup>1</sup> ; fatal colchicine toxicity has been reported with clarithromycin, a strong CYP3A4 inhibitor. Similarly, significant increase in colchicine plasma levels is anticipated with other strong CYP3A4 inhibitors.	Use colchicine with caution at reduced maximum dose of 0.3 mg twice daily with increased monitoring for adverse effects. In patients with renal or hepatic impairment, use of colchicine in conjunction with these drugs is contraindicated.
Moderate CYP3A4 inhibitors: amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, verapamil	Significant increase in colchicine plasma concentration is anticipated. Neuromuscular toxicity has been reported with diltiazem and verapamil interactions.	Use colchicine with caution at reduced maximum dose of 0.6 mg twice daily with increased monitoring for adverse effects. In patients with renal or hepatic impairment, use a maximum dose of 0.3 mg twice daily.
Strong P-gp Inhibitors e.g. Cyclosporine, ranolazine.	Significant increase in colchicine plasma levels <sup>1</sup> ; fatal colchicine toxicity has been reported with cyclosporine, a strong P-gp inhibitor. Similarly, significant increase in colchicine plasma levels is anticipated with other strong P-gp inhibitors.	Use colchicine with caution at reduced maximum dose of 0.3 mg twice daily with increased monitoring for adverse effects. In patients with renal or hepatic impairment, use of colchicine in conjunction with these drugs is contraindicated.

Pharmacy management systems are computer-based systems that are widely used by commercial pharmacies to manage prescriptions and to provide pharmacy and medical personnel with warnings and guidance regarding drugs being administered to individuals. Such systems typically provide alerts warning either or both of health care providers and patients when a drug that may be harmful to the particular patient is prescribed. For example, such systems can provide alerts warning that a patient has an allergy to a prescribed drug, or is receiving concomitant administration of a drug that can have a dangerous interaction with a prescribed drug. U.S. Pat. Nos. 5,758,095, 5,833,599, 5,845,255, 6,014,631, 6,067, 524, 6,112,182, 6,317,719, 6,356,873, and 7,072,840, each of which is incorporated herein by reference, disclose various pharmacy management systems and aspects thereof. Many pharmacy management systems are now commercially available, e.g., CENTRICITY Pharmacy from BDM Information Systems Ltd., General Electric Healthcare, Waukesha, Wis., Rx30 Pharmacy Systems from Transaction Data Systems, Inc., Ocoee, Fla., SPEED SCRIPT from Digital Simplistics,

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Inc., Lenexa, Ky., and various pharmacy management systems from OPUS-ISM, Hauppauge, N.Y.

In another aspect, herein disclosed are methods for using colchicine which methods involve the use of pharmacy management systems.

In one aspect, one such method comprises a pharmacy receiving a prescription for colchicine for a patient who is suffering from gout (e.g., acute gout flares or chronic gout) and who is concomitantly being treated with a second active agent (e.g., ketoconazole or ritonavir) that is an inhibitor of CYP3A and P-glycoprotein, followed by the pharmacy dispensing colchicine in response to receipt of the prescription, wherein the dispensing is preceded by entry into a first computer readable storage medium, in functional communication

with a computer, of a unique patient identifier for said patient and at least one drug identifier for colchicine linked to the patient identifier so as to indicate that colchicine is to be administered to the patient. The computer is programmed to issue a drug-drug interaction alert when the at least one drug identifier for colchicine is entered linked to the patient identifier so as to indicate that colchicine is to be administered to the patient and when the patient identifier is also linked to an identifier indicating that a second active agent (e.g., ketoconazole or ritonavir) that is an inhibitor of CYP3A4 or P-glycoprotein is being concomitantly administered to the patient. Upon entry of the at least one drug identifier for colchicine linked to the patient identifier, a drug-drug interaction alert is issued to one or more of a pharmacy technician, a pharmacist, or a pharmacy customer obtaining the colchicine, said alert indicating that a second active agent (e.g., ketoconazole or ritonavir) is being concomitantly administered to the patient and that prior to the colchicine being dispensed, the colchicine dosing regimen must be reviewed and, if necessary adjusted, so that when the colchicine is delivered to the phar-

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macy customer obtaining the colchicine it is delivered along with instructions for the colchicine to be taken in accordance with a dosing regimen of no more than one about 0.6 mg colchicine dose to start (e.g., following the onset of the acute gout attack or the first sign of a gout flare) followed by either: no additional colchicine doses within about 12, 24, 48, or 72 hours, or at least one additional colchicine dose within about 12 hours and no more frequently than once every hour and wherein each additional colchicine dose is no greater than about 0.6 mg, and wherein the patient ingests the colchicine as instructed.

The drug-drug interaction alert is preferably issued as one or both of a written warning on a display screen of the pharmacy management computer system, and a printed warning. The printed warning may be attached to or packaged with the dispensed prescription.

In one aspect, the identifier indicating that ketoconazole is being concomitantly administered to the patient is an identifier indicating that the second active agent is ketoconazole and is linked to at least one further identifier indicating that the ketoconazole is prescribed so that 200 mg of ketoconazole is to be ingested by the patient daily, in which case the dosing regimen for colchicine is preferably one about 0.6 mg colchicine dose to start, optionally followed by additional colchicine doses, e.g., 0, 1, 2, 3, or 4 additional colchicine doses within 24 hours of about 0.3 mg ingested every 1, 2, 3, 4, 5, 6, 7, 8, 9 10, 11, or 12 hours (e.g., every 2, 3, 4, 5, or 6 hours) after the preceding colchicine dose. In another embodiment, the identifier indicating that ketoconazole is being concomitantly administered to the patient is an identifier indicating that the second active agent is ketoconazole is linked to at least one further identifier, entered into a second computer readable storage medium in functional communication with a computer, the second storage medium being the same as or different from the first storage medium, and the further identifier indicating that the ketoconazole is prescribed so that about 200 mg of ketoconazole is to be ingested by the patient daily, in which case the colchicine dosing regimen is one about 0.6 mg colchicine dose to start, followed by an about 0.3 mg colchicine dose ingested every 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 hours (e.g., every six to eight hours) after the preceding colchicine dose. In one embodiment, the dosing regimen calls for the about 0.3 mg colchicine dose every six to eight hours. In another embodiment, the dosing regimen calls for one dose of the colchicine every eight to twelve hours.

In yet another preferred aspect, the identifier indicating that ketoconazole is being concomitantly administered to the patient is an identifier indicating that the second active agent is ketoconazole and is linked to at least one further identifier, entered into a second computer readable storage medium in functional communication with a computer, the second storage medium being the same as or different from the first storage medium, and the further identifier indicating that the ketoconazole is prescribed so that about 200 mg of ketoconazole is to be ingested by the patient daily and the dosing regimen is one about 0.3 mg colchicine dose to start, followed by an about 0.3 mg colchicine dose ingested every 2, 3, 4, 5, 6, 7, or 8 hours (e.g., every eight to twelve hours) after the preceding colchicine dose.

A preferred dosing regimen calls for ingestion of colchicine to be continued until a total of no more than 1.2 mg or 2.4 mg of colchicine has been ingested, after which ingestion of colchicine is to be stopped, e.g., for at least 2, 3, 4, 5, 6, or 7 days, or until a subsequent acute gout flare, or the first sign of a subsequent gout flare, occurs.

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In another aspect, the identifier indicating that ritonavir is being concomitantly administered to the patient is an identifier indicating that the second active agent is ritonavir and is linked to at least one further identifier indicating that the ritonavir is prescribed so that 200 or 1200 mg of ritonavir is to be ingested by the patient daily, in which case the dosing regimen for colchicine is preferably one about 0.6 mg colchicine dose to start, optionally followed by additional colchicine doses, e.g., 0, 1, 2, 3, or 4 additional colchicine doses within 24 hours of about 0.3 mg ingested every 1, 2, 3, 4, 5, 6, 7, 8, 9 10, 11, or 12 hours (e.g., every 2, 3, 4, 5, or 6 hours) after the preceding colchicine dose. In another embodiment, the identifier indicating that ritonavir is being concomitantly administered to the patient is an identifier indicating that the second active agent is ritonavir is linked to at least one further identifier, entered into a second computer readable storage medium in functional communication with a computer, the second storage medium being the same as or different from the first storage medium, and the further identifier indicating that the ritonavir is prescribed so that about 1200 mg of ritonavir is to be ingested by the patient daily, in which case the colchicine dosing regimen is one about 0.6 mg colchicine dose to start, followed by an about 0.3 mg colchicine dose ingested every 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 hours (e.g., every six to eight hours) after the preceding colchicine dose. In one embodiment, the dosing regimen calls for the about 0.3 mg colchicine dose every six to eight hours. In another embodiment, the dosing regimen calls for one dose of the colchicine every eight to twelve hours.

In yet another aspect, the identifier indicating that ritonavir is being concomitantly administered to the patient is an identifier indicating that the second active agent is ritonavir and is linked to at least one further identifier, entered into a second computer readable storage medium in functional communication with a computer, the second storage medium being the same as or different from the first storage medium, and the further identifier indicating that the ritonavir is prescribed so that about 1200 mg of ritonavir is to be ingested by the patient daily and the dosing regimen is one about 0.3 mg colchicine dose to start, followed by an about 0.3 mg colchicine dose ingested every 2, 3, 4, 5, 6, 7, or 8 hours (e.g., every eight to twelve hours) after the preceding colchicine dose.

Also disclosed herein is a dosage adjustment method for administering colchicine to a patient to treat a medical condition, the patient concomitantly treated with a second active agent. The second active agent may be, for example, ritonavir, ketoconazole, cyclosporine, verapamil, or diltiazem. The method comprises determining a first colchicine dosing regimen (the colchicine dosing regimen suitable for administration in the absence of co-administration with a second active agent, which dosing regimen may consist of one or more doses of colchicine); and determining a second active agent dosing regimen; and administering the second active agent to the patient at the second active agent dosing regimen while concomitantly administering colchicine to the patient according to a second colchicine dosing regimen, which may consist of one or more reduced colchicine doses. The second colchicine dosing regimen is a fraction of the first colchicine dosing regimen, where the fraction is obtained by administering reduced colchicine doses or by reducing the frequency of colchicine doses, and wherein the fraction is less than or equal to about  $\frac{2}{3}$  or less than or equal to about  $\frac{1}{2}$  or less than or equal to about  $\frac{1}{3}$ .

According to this embodiment, upon the administering the second active agent to the patient at the second active agent dosing regimen while concomitantly administering colchicine to the patient at the second colchicine dosing regimen,

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the therapeutic circulating level of colchicine is achieved in the patient. Preferably, the fraction is selected from  $\frac{1}{12}$ ,  $\frac{1}{6}$ ,  $\frac{1}{4}$ ,  $\frac{1}{3}$ ,  $\frac{5}{12}$ , and  $\frac{1}{2}$ , more preferably, the fraction is  $\frac{1}{3}$  or  $\frac{1}{2}$ . In one embodiment, if the second colchicine dosing regimen comprises a "first" colchicine dose, and one or more "subsequent" colchicine doses, each subsequent colchicine dose may be the same as the first dose, or a fraction of the first dose. The fraction is selected from about  $\frac{1}{12}$ , about  $\frac{1}{6}$ , about  $\frac{1}{4}$ , about  $\frac{1}{3}$ , about  $\frac{5}{12}$ , about  $\frac{1}{2}$ , and about  $\frac{7}{12}$ , e.g., about  $\frac{1}{2}$  or about  $\frac{2}{3}$ . In one example, the second colchicine dosing regimen is once-a-day, twice-a-day, three-times-a-day or four-times-a-day. In a variation of this example, the initial treatment day in, a second colchicine dosing regimen that lasts for more than one day, has one more dose administered than are administered each subsequent day.

Preferably the second active agent is selected from ketoconazole, cyclosporine, ritonavir, verapamil, or diltiazem. The specific conditions are selected from gout, FMF, thrombocytopenic purpura, and Behçet's disease. In one embodiment, the gout is an acute gout flare and the colchicine treatment schedule is an acute treatment schedule adapted for treatment of acute gout flares, or the gout is chronic gout, and the colchicine treatment schedule is a chronic treatment schedule adapted for prophylaxis, or prevention, of flares. In another embodiment, the fraction of colchicine administered to the patient concomitantly with a second active agent that is a CYP3A4 or P-gp inhibitor is  $\frac{1}{3}$  or  $\frac{1}{2}$  the original intended amount of colchicine and treatment with colchicine is initiated subsequent to or at the same time as initiation of treatment with the second active agent.

Colchicine is one of the most widely used drugs for treating familial Mediterranean fever (FMF). It has been reported that 5-10% of FMF patients do not show a beneficial response to colchicine administration. A polymorphism in the ABCB1 gene, the "ABCB1 3435 C to T polymorphism" has been reported to correlate with this lack of response to colchicine treatment, with patients with the homozygous TT genotype exhibiting the most pronounced "non-responder" phenotypes.

Accordingly, in another aspect, provided herein is a method for treating a patient suffering from FMF, which patient is a colchicine non-responder. Preferably, the patient is homozygous for the TT genotype of the ABCB1 3435 C to T polymorphism. The method entails the concomitant administration of a P-gp inhibitor and colchicine to the patient. Exemplary P-gp inhibitors include ketoconazole and ritonavir. Preferred dosages of the P-gp inhibitor for this purpose correspond to those called for in the prescribing information for the drug in question. For ketoconazole, an exemplary dosage is 200 mg per day. For ritonavir, an exemplary dosage is 200 or 1200 mg per day. Specific colchicine dosing regimens for this purpose are the same as used for treatment of FMF in responders, though the doses of colchicine administered may be increased as tolerated, e.g., up to two to three times the typical doses.

The following examples further illustrate aspects of this disclosure but should not be construed as in any way limiting its scope. In particular, the conditions are merely exemplary and can be readily varied by one of ordinary skill in the art.

## EXAMPLES

## Example 1

## Pharmacokinetic Study in Healthy Adults of Single vs. Multiple Oral Doses of Colchicine Tablets

This study was a single-center, open-label, single-sequence, two-period study to evaluate the pharmacokinetic

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profile of colchicine following single and multiple oral doses of colchicine tablets, 0.6 mg, in healthy volunteers.

In Period 1, study subjects received a 0.6-mg dose of colchicine after an overnight fast of at least 10 hours. In Period 2, subjects received a 0.6 mg dose of colchicine in the morning and the evening (approximately 12 hours later) for 10 days (steady state regimen). Subjects received a light breakfast served 60 minutes following dose administration in the morning and the evening dose was administered 90 minutes after an evening meal on Days 15 through 24 only. On Day 25, the colchicine dose was administered after an overnight fast of at least 10 hours and lunch was served 4 hours post-dose. Study periods were separated by a 14-day wash-out. Following the single dose and the last dose of the multiple dose regimen (beginning on the mornings of Day 1 and Day 25, respectively), blood samples were collected (6 mL each) from each subject within 1 hour prior to dosing and after dose administration at study hours 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 (while confined) and 36, 48, 72, and 96 (on an outpatient basis). Plasma concentrations of colchicine and its metabolites were determined using validated LC/MS-MS methods.

Thirteen healthy, non-smoking subjects with a mean age of 25.5 years (range 19 to 38 years) and within 15% of ideal body weight were enrolled in this study. All subjects completed both dosing periods according to protocol.

After a single dose, plasma concentrations are no longer quantifiable 24 hours post-dose in all but 1 subject. After the last dose of the steady state regimen, concentrations remained quantifiable for 48 to 72 hours. Review of individual subject data shows that no subject experienced a secondary colchicine peak, either following a single dose or upon multiple dosing.

All 2-O-demethylcolchicine (2-DMC) concentrations were below the level of quantitation (LOQ, 0.2 ng/mL) and only one sample from 1 subject (of 13 subjects) had a detectable 3-O-demethylcolchicine (3-DMC) concentration, which was near the level of quantitation. Therefore, metabolites are not discussed further.

In healthy adults, colchicine appears to be readily absorbed when given orally, reaching a mean maximum plasma concentration of 2.5 ng/mL in 1.5 hours after a single dose. The drug is distributed widely, with an apparent volume of distribution of 540 L, greatly exceeding total body water. The elimination half-life as calculated following a single oral dose is approximately 5 hours. Levels were not detectable by 24 hours post-dose and this is therefore not an accurate estimate. Pharmacokinetic parameter values are summarized in the table below.

Review of trough plasma concentrations indicates that steady state was attained by approximately the eighth day of dosing for most subjects. Colchicine may have a diurnal variation reflected in the observed C<sub>min</sub> concentrations at steady state. C<sub>min</sub> concentrations prior to the morning dose are approximately 12% higher than the C<sub>min</sub> concentrations prior to the evening dose (Day 23 and Day 24). The mean C<sub>min</sub> concentration observed on Day 25 was 0.907 ng/mL.

Colchicine accumulated following administration of multiple doses to an extent greater than expected. Exposure was nearly two-fold higher (approximately 1.7 based on AUC [Day 25 AUC<sub>0-∞</sub>/Day 1 AUC<sub>0-∞</sub>] and approximately 1.5 based on C<sub>max</sub> [Day 25 C<sub>max</sub>/Day 1 C<sub>max</sub>]). This observation could be attributable to an underestimation of AUC<sub>∞</sub> following a single dose. With the higher plasma levels that occur with repeated dosing, a longer terminal elimination half life is apparent, 26.6 hours. Pharmacokinetic parameter values are summarized in Tables 3-5.

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TABLE 3

Colchicine Pharmacokinetic Parameter Values Following Administration of A Single Oral Dose of Colchicine 0.6 mg in Healthy Adults (N = 13)						
	MEAN	STDEV	% CV	MEDIAN	MIN	MAX
AUC <sub>0-t</sub> (pg-hr/mL)	10494.66	3544.08	33.77	10560.90	4812.88	18091.85
AUC <sub>0-inf</sub> (pg-hr/mL)	12268.18	4422.08	36.05	11451.45	7252.66	23801.68
C <sub>max</sub> (pg/mL)	2450.15	702.11	28.66	2480.00	1584.00	3977.00
T <sub>max</sub> (hr)	1.50	0.54	36.00	1.50	1.00	3.00
K <sub>el</sub> (1/hr)	0.1829	0.0592	32.38	0.1992	0.0359	0.2443
T <sub>1/2</sub> (hr)	4.95	4.43	89.54	3.48	2.84	19.29

TABLE 4

Colchicine Pharmacokinetic Parameter Values Following Administration of Multiple (b.i.d.) Oral Doses of Colchicine 0.6 mg in Healthy Adults (N = 13)						
	MEAN	STDEV	% CV	MEDIAN	MIN	MAX
AUC <sub>0-t</sub> (pg-hr/mL)	43576.96	9333.26	21.42	41925.10	29328.78	58265.35
AUC <sub>0-τ</sub> (pg-hr/mL)	20366.61	3322.12	16.31	20423.08	13719.18	25495.25
AUC <sub>0-inf</sub> (pg-hr/mL)	54198.77	9214.54	17.00	54113.43	37599.76	67944.65
C <sub>max</sub> (pg/mL)	3553.15	843.45	23.74	3734.00	1977.00	4957.00
C <sub>min</sub> (pg/mL)	906.51	152.19	16.79	903.50	636.23	1149.67
C <sub>ave</sub> (pg/mL)	1697.22	276.84	16.31	1701.92	1143.26	2124.60
T <sub>max</sub> (hr)	1.31	0.60	45.61	1.00	0.50	3.00
K <sub>el</sub> (1/hr)	0.0267	0.0044	16.34	0.0261	0.0206	0.0333
T <sub>1/2</sub> (hr)	26.60	4.33	16.26	26.51	20.82	33.65

TABLE 5

Mean (% CV) Colchicine Pharmacokinetic Parameter Values Following Administration of Single and Multiple (b.i.d.) Oral Doses of Colchicine 0.6 mg in Healthy Adults		
	Vd/F (L)	CL/F (L/hr)
Colchicine 0.6-mg Single Dose (N = 13)		
Day 1	341 (54.4)	54.1 (31.0)
Colchicine 0.6 mg b.i.d. × 10 days		
Day 25	1150 (18.73)	30.3 (19.0)

CL = Dose/AUC<sub>0-t</sub> (Calculated from mean values)Vd = CL/K<sub>e</sub> (Calculated from mean values)

In tables, the parameter CL/F denotes the apparent total body clearance after administration, calculated as Total Dose/ Total AUC<sub>0-∞</sub>; and V<sub>d</sub>/F denotes the apparent total volume of distribution after administration, calculated as Total Dose/ (Total AUC<sub>0-∞</sub> × K<sub>el</sub>). FIG. 1 shows mean colchicine plasma concentrations following administration of single and multiple oral doses of colchicine 0.6 mg in healthy adults.

## Example 2

## Clinical Drug-Drug Interaction Study of Colchicine and Clarithromycin

A single-center, open-label, one sequence, two-period study was carried out in 23 healthy subjects. On Day 1, a single 0.6-mg dose of colchicine was administered. After completing a 21-day washout period, all subjects received 250 mg of clarithromycin administered twice daily for 7 days (Days 22 through 29), a sufficient dose and duration to inhibit CYP3A4 and Pgp. On the final day (Day 29), a single dose of colchicine was co-administered with the clarithromycin dose. When combined with steady-state clarithromycin, there is a significant increase in exposure to colchicine as compared to when colchicine is given alone: the mean C<sub>max</sub> and AUC<sub>0-t</sub> concentrations increased 167% and 250%, respectively. In addition, co-administration of clarithromycin and colchicine resulted in an increase of 233% in the plasma elimination half-life (t<sub>1/2</sub>) of colchicine and a 75% decrease in apparent clearance (CL/F). A summary of the mean (% CV) colchicine pharmacokinetic parameters for Day 1 (colchicine administered alone) and Day 29 (colchicine co-administered with steady-state clarithromycin) are given in the table below and illustrated in Table 5.

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TABLE 6

Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Clarithromycin in Healthy Adults		
Arithmetic Mean (% CV)		
Parameter (units)	Colchicine (N = 23)	Colchicine + Clarithromycin (N = 23)
AUC <sub>0-<math>t</math></sub> (ng · hr/mL)	12.37 (37.64)	41.95 (23.31)
AUC <sub>0-<math>\infty</math></sub> (ng · hr/mL)	15.53 (49.6)	52.62 (22.84)
C <sub>max</sub> (ng/mL)	2.84 (30.97)	8.44 (17.63)
T <sub>max</sub> (hr)*	1.50 (0.50-2.00)	1.00 (0.50-2.00)
CL/F (L/hr)	46.8 (43.68)	12.0 (23.75)

FIG. 2 shows a pharmacokinetic profile comparison of single-dose colchicine (0.6 mg, alone) and single-dose colchicine (0.6 mg) co-administered with steady-state clarithromycin in healthy adults. Based on the foregoing data, it is concluded that the dose of colchicine co-administered with clarithromycin should be reduced by  $\frac{2}{3}$ .

## Example 3

## Clinical Drug-Drug Interaction Study of Colchicine and Cyclosporine

This study was an open-label, non-randomized, single-center, one-sequence, two-period drug interaction study conducted in healthy male and female volunteers. Twenty-four (24) non-smoking, non-obese adult volunteers were enrolled. All subjects were dosed and studied as a single cohort, with each subject receiving the same treatment in a non-randomized fashion.

A single dose of colchicine, 0.6 mg, was administered alone on Day 1, and then co-administered with cyclosporine on Day 15. Cyclosporine was administered as a single-dose (1×100 mg capsule) on the morning of Day 15. A 14 day washout period was completed after the first colchicine dose on Day 1 and prior to the co-administration of colchicine and cyclosporine doses on Day 15.

Serial blood samples were collected by individual venipuncture up to 96 hours following drug administration on Day 1 and Day 15. Blood samples for determination of colchicine plasma concentrations were obtained at time zero (pre-dose) and after dose administration at 0.5, 1.0, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours post-dose on a confined basis. Subjects were then return to the clinic on a non-confined basis for continued blood sampling collection at 36, 48, 72, and 96 hours post-dose administration on Days 2-5 (Period 1) and Days 16-19 (Period 2). Cyclosporine plasma concentrations were not measured.

TABLE 7

Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Cyclosporine in Healthy Adults		
Arithmetic Mean (% CV)		
Parameter (units)	Colchicine (N = 23)	Colchicine + Cyclosporine (N = 23)
AUC <sub>0-<math>t</math></sub> (ng · hr/mL)	12.55	39.83
AUC <sub>0-<math>\infty</math></sub> (ng · hr/mL)	15.00	47.31
C <sub>max</sub> (ng/mL)	2.72	8.82

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TABLE 7-continued

Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Cyclosporine in Healthy Adults		
Arithmetic Mean (% CV)		
Parameter (units)	Colchicine (N = 23)	Colchicine + Cyclosporine (N = 23)
T <sub>max</sub> (hr)*	1.15	1.13
CL/F (L/hr)	48.24	13.42

FIG. 3 shows a pharmacokinetic profile comparison of single-dose colchicine (0.6 mg, alone) and single-dose colchicine (0.6 mg) co-administered with steady-state clarithromycin and steady-state cyclosporine in healthy adults. Based on the foregoing data, the dose of colchicine co-administered with cyclosporine should be reduced by approximately  $\frac{1}{2}$  to  $\frac{3}{4}$ .

## Example 4

## Clinical Drug-Drug Interaction Study of Colchicine and Ritonavir

An open-label, non-randomized, single-center, one-sequence, two-period drug interaction study was conducted in healthy male and female volunteers; there will be a 14-day washout between the two periods. Twenty-four (24) non-smoking non-obese adult volunteers were enrolled. All subjects were dosed and studied as a single cohort, with each subject receiving the same treatment in a non-randomized fashion.

All subjects received a single 0.6-mg dose of colchicine on Day 1 administered under standard fasting conditions, followed by a 14-day washout period completed on an outpatient basis. At discharge on Day 2, study subjects were instructed to return to the clinical site on the mornings and evenings of Days 15 through 18 to receive two daily dosage amounts of ritonavir (1×100 mg ritonavir capsule twice daily (every 12 hours) on Days 15-18) in a 'directly-observed' fashion; after taking the first dose of ritonavir, subjects remained in the clinic for observation for 1 hour post-dose administration on Day 15. On the evening of Day 18, study participants remained at the clinic for their final study confinement period. In the morning on Day 19, study subjects received a single 0.6 mg colchicine dose with a single 100 mg ritonavir dose and study subjects received the final 100 mg ritonavir dose 12 hours later in the evening on Day 19 under standard fasting conditions.

Serial blood samples were collected by individual venipuncture up to 96 hours following drug administration on Day 1 and Day 19. Blood samples for determination of colchicine plasma concentrations were obtained at time zero (pre-dose) and after dose administration at 0.5, 1.0, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours post-dose on an inpatient basis. Subjects returned to the clinic on an outpatient basis for continued blood sampling collection at 36, 48, 72, and 96 hours post-dose administration. Ritonavir plasma concentrations were not measured.

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TABLE 8

Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Ritonovir in Healthy Adults: ln-transformed data			
	Colchicine Alone	Colchicine + Ritonovir	% Ratio
$C_{max}$ (pg/mL), geometric mean	1798.37	4835.39	268.88
$AUC_{0-t}$ (pg · h/mL), geometric mean	7642.71	27793.08	363.65
$AUC_{\infty}$ (pg · h/mL), geometric mean	9551.74	33771.36	353.56

TABLE 9

Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Ritonavir in Healthy Adults			
Parameter (units)	Arithmetic Mean (% CV) Median (Range) for $T_{max}$		
	Colchicine + Ritonavir (N = 18)	Colchicine Alone (N = 18)	
$AUC_{0-t}$ (ng · hr/mL)	29.05 (30.76)	8.41 (47.46)	
$AUC_{0-\infty}$ (ng · hr/mL)	35.28 (29.79)	10.41 (45.48)	
$C_{max}$ (ng/mL)	4.99 (25.18)	1.87 (28.19)	
$T_{max}$ (hr)	1.5 (1-1.5)	1 (0.5-1.5)	
CL/F (L/hr)	18.59 (31.58)	67.93 (39.47)	

Following exposure to 100 mg b.i.d. ×5 days, there was a significant increase in exposure to a single 0.6-mg colchicine (approximately 245%). Mean peak colchicine concentration increased by approximately 170%. Total apparent oral clearance was decreased by 70% with co-administration.  $T_{max}$  is not affected. Elimination half-life could not be estimated accurately as plasma concentrations were not quantifiable after 24 hours.

FIG. 4 shows a pharmacokinetic profile comparison of single-dose colchicine (0.6 mg, alone) and single-dose colchicine (0.6 mg) co-administered with steady-state ritonavir and steady-state ketoconazole in healthy adults. Based on the foregoing data, the dose of colchicine co-administered with ritonavir should be reduced by approximately ½.

## Example 5

## Clinical Drug-Drug Interaction Study of Colchicine and Ketoconazole

This study was an open-label, non-randomized, single-center, one-sequence, two-period drug interaction study conducted in healthy male and female volunteers; there will be a 14-day washout between the two periods. Twenty-four (24) non-smoking, non-obese adult volunteers were enrolled.

A single dose of colchicine, 0.6 mg, was administered alone on Day 1, and then co-administered with ketoconazole on Day 19 (AM dose). Ketoconazole was administered for 5 consecutive days [200 mg twice daily (every 12 hours)] beginning on the morning of Day 15, with the last 200 mg ketoconazole dose administered on the evening on Day 19. Total study participation, exclusive of up to 28 days of screening, was approximately 24 days, during which subjects will be confined on two occasions for a total confinement of approximately 3 days.

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Serial blood samples were collected by individual venipuncture up to 96 hours following drug administration on Day 1 and Day 19. Blood samples for determination of colchicine plasma concentrations were obtained at time zero (pre-dose) and after dose administration at 0.5, 1.0, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours post-dose on an inpatient basis. Subjects then returned to the clinic on an outpatient basis for continued blood sampling collection at 36, 48, 72, and 96 hours post-dose administration. Ketoconazole plasma concentrations were not measured.

TABLE 10

Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Ketoconazole in Healthy Adults: ln-transformed data			
	Colchicine Alone	Colchicine + Ketoconazole	% Ratio
$C_{max}$ (pg/mL), geometric mean	2598.28	5078.50	195.46
$AUC_{0-t}$ (pg · h/mL), geometric mean	11087.99	33223.80	299.64
$AUC_{\infty}$ (pg · h/mL), geometric mean	13185.92	42143.00	319.61

TABLE 11

Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Ketoconazole in Healthy Adults			
Parameter (units)	Arithmetic Mean (% CV)		
	Colchicine (N = 23)	Colchicine + Ketoconazole (N = 23)	
$AUC_{0-t}$ (pg · hr/mL)	11988.61	34382.82	
$AUC_{0-\infty}$ (pg · hr/mL)	14314.09	43688.90	
$C_{max}$ (pg/mL)	2779.08	5266.92	
$T_{max}$ (hr)*	1.00	1.02	
CL/F (L/hr)	49301.09	14797.94	

\*Median (Range) for  $T_{max}$

Following administration of ketoconazole 200 mg b.i.d. ×5 days, there was a significant increase in exposure to a single oral dose of colchicine 0.6 mg ( $C_{max}$  and  $AUC_{0-t}$  increased by 90% and 190%, respectively, and  $AUC_{0-\infty}$  increased by about 205%). Total apparent oral clearance decreased by 70% with co-administration. Elimination half-life could not be estimated accurately as plasma concentrations were not quantifiable after 24 hours.

FIG. 4 shows a pharmacokinetic profile comparison of single-dose colchicine (0.6 mg, alone) and single-dose colchicine (0.6 mg) co-administered with steady-state ritonavir and steady-state ketoconazole in healthy adults. Based on the foregoing data, the dose of colchicine co-administered with ketoconazole should be reduced by approximately ½.

## Example 6

## Clinical Drug-Drug Interaction Study of Colchicine and Azithromycin

This study was an open-label, non-randomized, single-center, one-sequence, two-period drug interaction study conducted in healthy male and female volunteers; there was a

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14-day washout between the two periods. Twenty-four (24) non-smoking, non-obese adult volunteers were enrolled. All subjects were dosed and studied as a single cohort, with each subject receiving the same treatment in a non-randomized fashion.

A single dose of colchicine, 0.6 mg, was administered alone on Day 1, and then co-administered with the azithromycin on Day 19. Azithromycin was administered for 5 consecutive days (2x250 mg once daily [Day 15 only] and then 1x250 mg once daily Days 16-19) beginning on the morning of Day 15, with the last 250 mg azithromycin dose administered on the morning on Day 19. Total study participation, exclusive of up to 28 days of screening, was approximately 24 days, during which subjects were confined on two occasions for a total confinement of approximately 3 days.

Serial blood samples were collected by individual venipuncture up to 96 hours following drug administration on Day 1 and Day 19. Blood samples for determination of colchicine plasma concentrations were obtained at time zero (pre-dose) and after dose administration at 0.5, 1.0, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours post-dose on an inpatient basis. Subjects returned to the clinic on an outpatient basis for continued blood sampling collection at 36, 48, 72, and 96 hours post-dose administration. Azithromycin plasma concentrations were not measured.

TABLE 12

Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Azithromycin in Healthy Adults			
	Colchicine Alone	Colchicine + Azithromycin	% Ratio
$C_{max}$ (pg/mL), geometric mean	2535.94	2856.22	112.63
$AUC_{0-t}$ (pg · hr/mL), geometric mean	10971.51	16090.52	146.66
$AUC_{\infty}$ (pg · hr/mL), geometric mean	12931.80	18312.83	141.61

TABLE 13

Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Azithromycin in Healthy Adults		
Arithmetic Mean (% CV) Median (Range) for $T_{max}$		
Parameter (units)	Colchicine + Azithromycin (N = 21)	Colchicine Alone (N = 21)
$AUC_{0-t}$ (ng · hr/mL)	17.16 (37.78)	11.98 (45.81)
$AUC_{0-\infty}$ (ng · hr/mL)	19.61 (39.15)	14.13 (46.73)
$C_{max}$ (ng/mL)	3.05 (39.54)	2.74 (41.52)
$T_{max}$ (hr)	1.5 (0.5-3)	1.0 (0.5-3)
$t_{1/2}$ (hr)	6.71 (68.34) <sup>1</sup>	6.07 (66.15) <sup>1</sup>
CL/F (L/hr)	35.01 (37.26)	50.24 (40.31)

Following administration of azithromycin 500 mg on Day 1 followed by 250 mgx4 days, exposure to colchicine is increased (approximately 46% for  $AUC_{0-t}$  and approximately 40% for  $AUC_{0-\infty}$ ). Mean peak colchicine concentration increased by approximately 12% and total apparent oral clearance decreased approximately 30% with co-administration.  $T_{max}$  was not affected.

FIG. 5 shows a pharmacokinetic profile comparison of single-dose colchicine (0.6 mg, alone) and single-dose

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colchicine (0.6 mg) co-administered with steady-state azithromycin and steady-state diltiazem in healthy adults.

## Example 7

## Clinical Drug-Drug Interaction study of Colchicine and Diltiazem

This study was an open-label, non-randomized, single-center, one-sequence, two-period drug interaction study conducted in healthy male and female volunteers. Twenty-four (24) non-smoking, non-obese adult volunteers were enrolled. All subjects were dosed and studied as a single cohort, with each subject receiving the same treatment in a non-randomized fashion.

As single dose of colchicine, 0.6 mg, was administered alone on Day 1, and then co-administered with diltiazem ER on Day 21. Diltiazem ER was administered for 7 consecutive days (1x240 mg capsule once daily on Days 15-21) beginning on the morning of Day 15, with the last 240 mg diltiazem ER dose administered on the morning on Day 21. A 14-day washout period was completed after the first colchicine dose on Day 1 and prior to the administration of the first diltiazem ER dose on Day 15.

Serial blood samples were collected by individual venipuncture up to 96 hours following drug administration on Day 1 and Day 21. Blood samples for determination of colchicine plasma concentrations were obtained at time zero (pre-dose) and after dose administration at 0.5, 1.0, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours post-dose on an inpatient basis. Subjects returned to the clinic on an outpatient basis for continued blood sampling collection at 36, 48, 72, and 96 hours post-dose administration. Diltiazem plasma concentrations were not measured.

TABLE 14

Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Diltiazem in Healthy Adults			
	Colchicine Alone	Colchicine + Diltiazem	% Ratio
$C_{max}$ (pg/mL), geometric mean	2006.42	2583.22	128.75
$AUC_{0-t}$ (pg · h/mL), geometric mean	9154.55	15740.37	171.94
$AUC_{\infty}$ (pg · h/mL), geometric mean	11022.30	19902.98	180.57

TABLE 15

Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Diltiazem in Healthy Adults		
Arithmetic Mean (% CV) Median (Range) for $T_{max}$		
Parameter (units)	Colchicine + Diltiazem (N = 20)	Colchicine Alone (N = 20)
$AUC_{0-t}$ (ng · hr/mL)	17.73	10.04
$AUC_{0-\infty}$ (ng · hr/mL)	22.49	12.03
$C_{max}$ (ng/mL)	2.80	2.17
$T_{max}$ (hr)	1.48	1.15
$t_{1/2}$ (hr)	12.50	5.51
CL/F (L/hr)	463.49	395.83

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FIG. 5 shows a pharmacokinetic profile comparison of single-dose colchicine (0.6 mg, alone) and single-dose colchicine (0.6 mg) co-administered with steady-state azithromycin and steady-state diltiazem in healthy adults.

## Example 8

## Clinical Drug-Drug Interaction Study of Colchicine and Verapamil

This study was an open-label, non-randomized, single-center, one-sequence, two-period drug interaction study conducted in healthy male and female volunteers. Twenty-four (24) non-smoking, non-obese adult volunteers were enrolled. All subjects were dosed and studied as a single cohort, with each subject receiving the same treatment in a non-randomized fashion.

A single dose of colchicine, 0.6 mg, was administered alone on Day 1, and then co-administered with verapamil HCl ER on Day 19. Verapamil HCl ER was administered for 5 consecutive days (1x240 mg tablet once daily on Days 15-19) beginning on the morning of Day 15, with the last 240 mg verapamil HCl ER dose administered on the morning on Day 19. A 14-day washout period was completed after the first colchicine dose on Day 1 and prior to the administration of the first verapamil HCl ER dose on Day 15.

Serial blood samples were collected by individual venipuncture up to 96 hours following drug administration on Day 1 and Day 19. Blood samples for determination of colchicine plasma concentrations were obtained at time zero (pre-dose) and after dose administration at 0.5, 1.0, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours post-dose on a confined basis. Subjects returned to the clinic on a non-confined basis for continued blood sampling collection at 36, 48, 72, and 96 hours post-dose administration on Days 2-5 (Period 1) and Days 20-23 (Period 2). Verapamil plasma concentrations were not measured.

TABLE 16

Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Verapamil in Healthy Adults			
	Colchicine Alone	Colchicine + Verapamil	% Ratio
$C_{max}$ (pg/mL), geometric mean	2768.77	3639.68	131.45
$AUC_{0-\infty}$ (pg · h/mL), geometric mean	12256.40	23889.21	194.94
$AUC_{\infty}$ (pg · h/mL), geometric mean	14415.79	29556.75	205.03

TABLE 17

Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Verapamil in Healthy Adults		
Parameter (units)	Arithmetic Mean (% CV) Median (Range) for $T_{max}$	
	Colchicine + Verapamil (N = 24)	Colchicine Alone (N = 24)
$AUC_{0-\infty}$ (ng · hr/mL)	24.64	13.09
$AUC_{0-\infty}$ (ng · hr/mL)	30.59	15.37
$C_{max}$ (ng/mL)	3.85	2.97
$T_{max}$ (hr)	1.15	1.22

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TABLE 17-continued

Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Verapamil in Healthy Adults		
Parameter (units)	Arithmetic Mean (% CV) Median (Range) for $T_{max}$	
	Colchicine + Verapamil (N = 24)	Colchicine Alone (N = 24)
$t_{1/2}$ (hr)	17.17	6.24
CL/F (L/hr)	21.01	43.93

Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. The endpoints of all ranges directed to the same component or property are inclusive and independently combinable.

All methods described herein can be performed in a suitable order unless otherwise indicated or clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., “such as”) herein is intended to better illuminate the disclosure and is non-limiting unless otherwise specified. No language in the specification should be construed as indicating that any non-claimed element as essential to the practice of the claimed embodiments. Unless defined otherwise, technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this disclosure belongs. The terms wt %, weight percent, percent by weight, etc. are equivalent and interchangeable.

In the specification and claims that follow, references will be made to a number of terms which shall be defined to have the following meaning.

The terms “a” and “an” do not denote a limitation of quantity, but rather denote the presence of at least one of the referenced item. The term “or” means “and/or”. The terms “comprising”, “having”, “including”, and “containing” are to be construed as open-ended terms (i.e., meaning “including, but not limited to”).

“Concomitant” and “concomitantly” as used herein refer to the administration of at least two drugs to a patient either simultaneously or within a time period during which the effects of the first administered drug are still operative in the patient. Thus, if the first drug is, e.g., clarithromycin and the second drug is colchicine, the concomitant administration of the second drug can occur as much as one to two weeks, preferably within one to seven days, after the administration of the first drug. This is because clarithromycin can exert a long-lasting inhibition of CYP3A isozymes so that CYP3A activity in the patient may not return to pre-clarithromycin-administration levels for as much as two weeks after the cessation of clarithromycin administration. If colchicine is the first drug, administration of a second drug would be concomitant if done within 1 to 2 days, preferably 12 to 24 hours.

A “dose” means the measured quantity of a drug to be taken at one time by a patient.

A “dosage amount” means an amount of a drug suitable to be taken during a fixed period, usually during one day (i.e. daily). A “daily dosage amount” is the total dosage amount taken in one day, that is, a 24 hour period.

“Dosing regimen” means the dose of a drug taken at a first time by a patient and the interval (time or symptomatic) and

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dosage amounts at which any subsequent doses of the drug are taken by the patient. Each dose may be of the same or different.

A "patient" means a human or non-human animal in need of medical treatment. Medical treatment can include treatment of an existing condition, such as a disease or disorder, prophylactic or preventative treatment, or diagnostic treatment. In preferred embodiments the patient is human.

"Providing" means giving, administering, selling, distributing, transferring (for profit or not), manufacturing, compounding, or dispensing.

"Risk" means the probability or chance of adverse reaction, injury, or other undesirable outcome arising from a medical treatment. An "acceptable risk" means a measure of the risk of harm, injury, or disease arising from a medical treatment that will be tolerated by an individual or group. Whether a risk is "acceptable" will depend upon the advantages that the individual or group perceives to be obtainable in return for taking the risk, whether they accept whatever scientific and other advice is offered about the magnitude of the risk, and numerous other factors, both political and social. An "acceptable risk" of an adverse reaction means that an individual or a group in society is willing to take or be subjected to the risk that the adverse reaction might occur since the adverse reaction is one whose probability of occurrence is small, or whose consequences are so slight, or the benefits (perceived or real) of the active agent are so great. An "unacceptable risk" of an adverse reaction means that an individual or a group in society is unwilling to take or be subjected to the risk that the adverse reaction might occur upon weighing the probability of occurrence of the adverse reaction, the consequences of the adverse reaction, and the benefits (perceived or real) of the active agent. "At risk" means in a state or condition marked by a high level of risk or susceptibility.

Pharmacokinetic parameters referred to herein describe the in vivo characteristics of drug (or a metabolite or a surrogate marker for the drug) over time. These include plasma concentration (C), as well as  $C_{max}$ ,  $C_n$ ,  $C_{24}$ ,  $T_{max}$ , and AUC. " $C_{max}$ " is the measured plasma concentration of the active agent at the point of maximum, or peak, concentration. " $C_{min}$ " is the measured plasma concentration of the active agent at the point of minimum concentration. " $C_n$ " is the measured plasma concentration of the active agent at about n hours after administration. " $C_{24}$ " is the measured plasma concentration of the active agent at about 24 hours after administration. The term " $T_{max}$ " refers to the time from drug administration until  $C_{max}$  is reached. "AUC" is the area under the curve of a graph of the measured plasma concentration of an active agent vs. time, measured from one time point to another time point. For example  $AUC_{0-t}$  is the area under the curve of plasma concentration versus time from time 0 to time t, where time 0 is the time of initial administration of the drug. Time t can be the last time point with measurable plasma concentration for an individual formulation. The  $AUC_{0-\infty}$ ,  $AUC_{\infty}$  or  $AUC_{0-inf}$  is the calculated area under the curve of plasma concentration versus time from time 0 to time infinity. In steady-state studies,  $AUC_{0-\tau}$  is the area under the curve of plasma concentration over the dosing interval (i.e., from time 0 to time  $\tau$  (tau), where tau is the length of the dosing interval. Other pharmacokinetic parameters are the parameter  $K_e$  or  $K_d$ , the terminal elimination rate constant calculated from a semi-log plot of the plasma concentration versus time curve;  $t_{1/2}$  the terminal elimination half-life, calculated as  $0.693/K_{el}$ .  $CL/F$  denotes the apparent total body clearance after administration, calculated as Total Dose/Total  $AUC_{\infty}$ ; and  $V_{area}/F$  denotes the apparent total volume of distribution after administration, calculated as Total Dose/(Total  $AUC_{\infty} \times K_{el}$ ).

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"Side effect" means a secondary effect resulting from taking a drug. The secondary effect can be a negative (unfavorable) effect (i.e., an adverse side effect) or a positive (favorable) effect.

The most frequently reported adverse side effects to colchicine therapy are gastrointestinal, specifically abdominal pain with cramps, diarrhea, nausea, and vomiting. Less frequently or rarely reported adverse side effects associated with colchicine therapy include anorexia, agranulocytosis, allergic dermatitis, allergic reactions, alopecia, angioedema, aplastic anemia, bone marrow depression, myopathy, neuropathy, skin rash, thrombocytopenic disorder, and urticaria.

Whether a patient experiences an adverse side effect can be determined by obtaining information from the patient regarding onset of certain symptoms which may be indicative of the adverse side effect, results of diagnostic tests indicative of the adverse side effect, and the like.

Embodiments are described herein, including the best modes known to the inventors. Variations of such embodiments will become apparent to those of ordinary skill in the art upon reading the foregoing description. The skilled artisan is expected to employ such variations as appropriate, and the disclosed methods are expected to be practiced otherwise than as specifically described herein. Accordingly, all modifications and equivalents of the subject matter recited in the claims appended hereto are included to the extent permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed unless otherwise indicated herein or otherwise clearly contradicted by context.

What is claimed is:

1. A method of treating a patient with colchicine, comprising

orally administering an adjusted daily dosage amount of colchicine to the patient who is receiving concomitant administration of ketoconazole,

wherein the adjusted daily dosage amount of colchicine is 25% to 50% of an intended daily dosage amount of colchicine, and

wherein the intended daily dosage amount of colchicine is a dosage amount suitable for the patient if the patient were not receiving concomitant ketoconazole.

2. The method of claim 1, wherein the treating is for the prophylaxis of gout flares, and wherein the intended daily dosage amount of colchicine suitable for the patient if the patient were not receiving concomitant ketoconazole is 0.6 mg twice daily or 0.6 mg once daily.

3. The method of claim 1, wherein the treating is for acute gout flares, and wherein the intended daily dosage amount of colchicine suitable for the patient if the patient were not receiving concomitant ketoconazole is 1.2 mg at the first sign of flare, followed by 0.6 mg one hour later, dose to be repeated no earlier than 3 days.

4. The method of claim 1, wherein the treating is for familial Mediterranean fever

wherein the adjusted daily dosage amount of colchicine is a maximum colchicine dosage amount of 0.6 mg of colchicine per day which is a reduction from the intended daily dosage amount of colchicine in the absence of concomitant ketoconazole wherein the intended daily dosage amount is a maximum daily dosage amount as follows:

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Age	Daily dosage amount	
	Usual	Maximum
Adults and children >12 years	1.2 mg	2.4 mg
Children >6 to 12 years	0.9 mg	1.8 mg
Children 4 to 6 years	0.3 mg	1.8 mg.

5. The method of claim 2, wherein the adjusted daily dosage amount of colchicine is 25% of a 0.6 mg twice daily intended dose. 10

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6. The method of claim 2, wherein the adjusted daily dosage amount of colchicine is 25% of a 0.6 mg once daily intended dose.

7. The method of claim 1, wherein the concomitantly administered dose of ketoconazole is 200 mg twice per day.

8. The method of claim 3, wherein the adjusted daily dosage amount is about 50% of the intended daily dosage amount.

\* \* \* \* \*

UNITED STATES PATENT AND TRADEMARK OFFICE  
**CERTIFICATE OF CORRECTION**

PATENT NO. : 7,964,648 B2  
APPLICATION NO. : 12/688038  
DATED : June 21, 2011  
INVENTOR(S) : Matthew W. Davis

Page 1 of 5

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page:

Item (56), under "OTHER PUBLICATIONS", in column 2, line 5, delete "COLCYRS" and insert -- COLCRYS --, therefor.

On page 2, under "OTHER PUBLICATIONS", in column 2, line 3, delete "Drugs.com;" "Colchicine" and insert -- Drugs.com; "Colchicine --, therefor.

In column 1, line 11, delete "Dec. 17, 2008" and insert -- January 14, 2009 --, therefor.

In column 2, lines 20-21, delete "3-demethylchochicine" and insert -- 3-demethylcolchicine --, therefor.

In column 3, line 6, delete "in a" and insert -- in an --, therefor.

In column 3, line 49, delete "that that" and insert -- that --, therefor.

In column 4, line 38, delete "■" and insert -- □ --, therefor.

In column 4, line 44, delete "●" and insert -- ○ --, therefor.

In column 4, line 51, delete "▲" and insert -- Δ --, therefor.

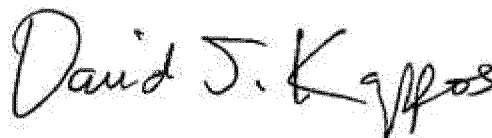
In column 4, line 51, delete "●" and insert -- ○ --, therefor.

In column 4, line 52, delete "■" and insert -- □ --, therefor.

In column 4, line 58, delete "▲" and insert -- Δ --, therefor.

In column 4, line 58, delete "●" and insert -- ○ --, therefor.

Signed and Sealed this  
Twentieth Day of November, 2012

A handwritten signature in black ink, reading "David J. Kappos". The signature is written in a cursive, flowing style with a large initial "D".

David J. Kappos  
*Director of the United States Patent and Trademark Office*

**CERTIFICATE OF CORRECTION (continued)**

Page 2 of 5

**U.S. Pat. No. 7,964,648 B2**

In column 4, line 59, delete “■” and insert -- □ --, therefor.

In column 4, line 66, delete “▲” and insert -- Δ --, therefor.

In column 4, line 66, delete “●” and insert -- ○ --, therefor.

In column 4, line 67, delete “■” and insert -- □ --, therefor.

In column 5, line 64, after “effect” insert -- . --.

In column 6, line 52, delete “in a” and insert -- in --, therefor.

In column 7, line 31, delete “0.6mg” and insert -- 0.6 mg --, therefor.

In column 7, line 33, delete “0.6mg” and insert -- 0.6 mg --, therefor.

In column 7, line 35, delete “0.6mg” and insert -- 0.6 mg --, therefor.

In column 8, line 62, after “may” insert -- be --.

In column 8, line 65, delete “wherein the” and insert -- the --, therefor.

In column 9, line 9, after “amount” insert -- is --.

In column 9, line 37, after “may” insert -- be --.

In column 9, line 40, delete “wherein the” and insert -- the --, therefor.

In column 9, line 50, after “amount” insert -- is --.

In column 10, line 12, after “may” insert -- be --.

In column 10, line 15, delete “wherein the” and insert -- the --, therefor.

In column 10, line 26, after “amount” insert -- is --.

In column 10, line 66, after “may” insert -- be --.

In column 11, line 8, after “amount” insert -- is --.

In column 12, line 42, delete “amount of” and insert -- amount for --, therefor.

In column 12, line 49, before “Colchicine” insert -- Table 2 --.

In column 13, line 20, delete “levels<sup>1</sup>” and insert -- levels --, therefor.

**CERTIFICATE OF CORRECTION (continued)**

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In column 13, line 37, delete “levels<sup>1</sup>” and insert -- levels --, therefor.

In column 13, line 62, after “thereof” insert -- . --.

In column 15, line 28, delete “9” and insert -- 9 --, therefor.

In column 16, line 11, delete “9” and insert -- 9 --, therefor.

In column 16, line 64, delete “the administering” and insert -- administering --, therefor.

In column 18, line 27, delete “are” and insert -- were --, therefor.

In column 18, line 37, delete “3-O-demethylcolchicine” and insert -- 3-O-demethylcolchicine --, therefor.

In column 18, line 53, delete “Cmin” and insert --  $C_{\min}$  --, therefor.

In column 18, line 54, delete “Cmin” and insert --  $C_{\min}$  --, therefor.

In column 18, line 55, delete “Cmin” and insert --  $C_{\min}$  --, therefor.

In column 18, line 57, delete “Cmin” and insert --  $C_{\min}$  --, therefor.

In column 18, line 62, delete “Cmax” and insert --  $C_{\max}$  --, therefor.

In column 18, line 63, delete “AUC $\infty$ ” and insert -- AUC $\infty$  --, therefor.

In column 19, line 9, delete “Cmax” and insert --  $C_{\max}$  --, therefor.

In column 19, line 11, delete “Tmax” and insert --  $T_{\max}$  --, therefor.

In column 19, line 49, delete “Vd/F” and insert --  $V_d/F$  --, therefor.

In column 19, line 59, delete “Vd = CL/Ke” and insert --  $V_d = CL/K_e$  --, therefor.

In column 19, line 63, delete “AUC<sub>0- $\tau$ ;</sub>” and insert -- AUC<sub>0- $\tau$ ;</sub> --, therefor.

In column 20, line 54, delete “Pgp.” and insert -- P-gp. --, therefor.

In column 20, line 62, delete “(t<sub>1/2</sub>)” and insert -- (t<sub>1/2</sub>) --, therefor.

In column 20, lines 66-67, after “below” delete “and illustrated in Table 5”.

In column 21, line 13, after “T<sub>max</sub> (hr)” delete “\*”.

**CERTIFICATE OF CORRECTION (continued)**

Page 4 of 5

**U.S. Pat. No. 7,964,648 B2**

In column 21, lines 48-49, delete “were then return” and insert -- then returned --, therefor.

In column 21, line 60, after “Arithmetic Mean” delete “(% CV)”.

In column 22, line 6, after “Arithmetic Mean” delete “(% CV)”.

In column 22, line 12, after “ $T_{\max}$  (hr)” delete “\*”.

In column 22, line 33, delete “will be” and insert -- was --, therefor.

In column 22, line 35, after “smoking” insert -- , --.

In column 23, line 4, delete “Ritonovir” and insert -- Ritonavir --, therefor.

In column 23, line 4, delete “In” and insert -- In --, therefor.

In column 23, line 7, delete “Ritonovir” and insert -- Ritonavir --, therefor.

In column 23, line 55, delete “will be” and insert -- was --, therefor.

In column 23, lines 65-66, delete “will be” and insert -- were --, therefor.

In column 24, line 7, delete “returnee” and insert -- returned --, therefor.

In column 24, line 33, after “Arithmetic Mean” delete “(% CV)”.

In column 24, line 42, after “\*Median”, delete “(Range)”.

In column 25, line 56, delete “(68.34)<sup>1</sup>” and insert -- (68.34) --, therefor.

In column 25, line 56, delete “(66.15)<sup>1</sup>” and insert -- (66.15) --, therefor.

In column 26, line 16, delete “As” and insert -- A --, therefor.

In column 26, line 56, after “Arithmetic Mean” delete “(% CV)”.

In column 26, line 58, after “Median”, delete “(Range)”.

In column 27, line 58, after “Arithmetic Mean” delete “(% CV)”.

In column 27, line 60, after “Median”, delete “(Range)”.

In column 28, line 7, after “Arithmetic Mean” delete “(% CV)”.

**CERTIFICATE OF CORRECTION (continued)**

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In column 28, line 8, after “Median”, delete “(Range)”.

In column 29, line 61, delete “ $K_d$ ” and insert --  $K_{el}$  --, therefor.

# EXHIBIT E

US007981938B2

(12) **United States Patent**  
**Davis**(10) **Patent No.:** **US 7,981,938 B2**(45) **Date of Patent:** **\*Jul. 19, 2011**(54) **COLCHICINE COMPOSITIONS AND METHODS**(75) Inventor: **Matthew W. Davis**, Erwinna, PA (US)(73) Assignee: **Mutual Pharmaceutical Company, Inc.**, Philadelphia, PA (US)

(\*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **12/687,406**(22) Filed: **Jan. 14, 2010**(65) **Prior Publication Data**

US 2010/0105780 A1 Apr. 29, 2010

**Related U.S. Application Data**

(63) Continuation of application No. 12/545,377, filed on Aug. 21, 2009, which is a continuation of application No. 12/465,210, filed on May 13, 2009, and a continuation of application No. 12/407,980, filed on Mar. 20, 2009, which is a continuation of application No. 12/246,034, filed on Oct. 6, 2008.

(60) Provisional application No. 60/977,796, filed on Oct. 5, 2007, provisional application No. 61/090,965, filed on Aug. 22, 2008.

(51) **Int. Cl.****A01N 37/18** (2006.01)**A61K 31/16** (2006.01)**C07C 233/00** (2006.01)**C07C 235/00** (2006.01)**C07C 237/00** (2006.01)**C07C 239/00** (2006.01)**C07C 211/00** (2006.01)**C07C 205/00** (2006.01)**C07C 207/00** (2006.01)(52) **U.S. Cl.** ..... **514/629**; 564/123; 564/308; 564/427; 568/306(58) **Field of Classification Search** ..... 514/629; 564/123, 308, 427; 568/306

See application file for complete search history.

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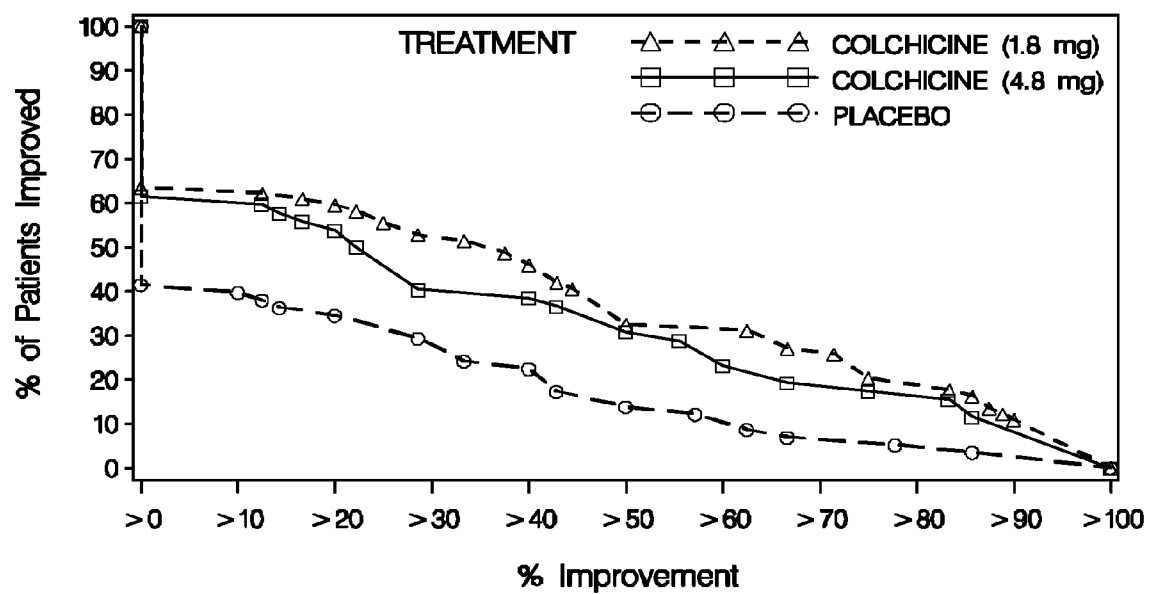
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\* cited by examiner

*Primary Examiner* — Sreeni Padmanabhan*Assistant Examiner* — Kara R McMillian(74) *Attorney, Agent, or Firm* — Cantor Colburn LLP(57) **ABSTRACT**

Stable ultrapure colchicine compositions comprising ultrapure colchicine and a pharmaceutically acceptable excipient are described. The compositions can be tablets. Methods for preparing such compositions and methods of use are also disclosed. Methods of treating gout flares with colchicine compositions are also disclosed.

**1 Claim, 1 Drawing Sheet**

**U.S. Patent****Jul. 19, 2011****US 7,981,938 B2****FIGURE 1**

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COLCHICINE COMPOSITIONS AND  
METHODSCROSS REFERENCE TO RELATED  
APPLICATION

This application is a continuation of U.S. application Ser. No. 12/545,377, filed Aug. 21, 2009; which is a continuation of U.S. application Ser. No. 12/465,210, filed May 13, 2009, and a continuation of U.S. application Ser. No. 12/407,980, filed Mar. 20, 2009, which is a continuation of U.S. application Ser. No. 12/246,034, filed Oct. 6, 2008, which claims the benefit of U.S. Provisional Application Ser. No. 60/977,796 filed Oct. 5, 2007 and U.S. Provisional Application Ser. No. 61/090,965 filed Aug. 22, 2008; each of the above-named applications is hereby incorporated by reference in its entirety.

## BACKGROUND

This application relates to colchicine compositions for therapeutic purposes, specifically ultrapure colchicine, and methods of making and using the colchicine compositions.

Colchicine, chemical name (–)-N-[7S,12aS)-1,2,3,10-tetramethoxy-9-oxo-5,6,7,9-tetrahydrobenzo[a]heptalen-7-yl]-acetamide, is a pale yellow powder soluble in water in 1:25 dilution.

Colchicine is an alkaloid found in extracts of certain plants such as *Colchicum autumnale* and *Gloriosa superba*. Colchicine arrests cell division in animals and plants. It has adversely affected spermatogenesis in humans and in some animal species under certain conditions.

Gout (or gouty arthritis) is a disease caused by a build up of uric acid due to an overproduction of uric acid or a reduced ability of the kidney to get rid of uric acid. It is more common in males, postmenopausal women, and people with high blood pressure. Heavy alcohol use, diabetes, obesity, sickle cell anemia, and kidney disease also increase the risk. The condition may also develop in people who take drugs that interfere with uric acid excretion.

In gout, monosodium urate or uric acid crystals are deposited on the articular cartilage of joints, tendons, and surrounding tissues due to elevated concentrations of uric acid in the blood stream. This provokes an inflammatory reaction of these tissues. Gout is characterized by excruciating, sudden, unexpected, burning pain, as well as swelling, redness, warmth, and stiffness in the affected joint. Low-grade fever may also be present. The patient usually suffers from two sources of pain. The crystals inside the joint cause intense pain whenever the affected area is moved. The inflammation of the tissues around the joint also causes the skin to be swollen, tender and sore if it is even slightly touched. For example, a blanket or even the lightest sheet draping over the affected area could cause extreme pain.

Acute gouty arthritis (alternatively referred to as a gout flare or a gout attack) is a sudden attack of pain in affected joints, especially in the feet and legs. Chronic gout involves repeated attacks of joint pain.

In acute gouty arthritis, symptoms develop suddenly and usually involve only one or a few joints. The big toe, knee, or ankle joints are most often affected. The pain frequently starts during the night and is often described as throbbing, crushing, or excruciating. The joint appears infected with signs of warmth, redness, and tenderness. The attacks of painful joints may go away in several days, but may return from time to time. Subsequent attacks usually last longer. Some people

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may progress to chronic gout (chronic gouty arthritis), while others may have no further attacks.

If several attacks of gout occur each year, it can lead to joint deformity and limited motion in joints. Uric acid deposits, called tophi, develop in cartilage tissue, tendons, and soft tissues. These tophi usually develop only after a patient has suffered from the disease for many years. Deposits also can occur in the kidneys, leading to chronic kidney failure.

Colchicine can be used for treating adults with acute gouty arthritis and pain in attacks of acute gouty arthritis, and also can be used beneficially for treating adults with chronic gout for prophylaxis of acute gout flares. Although its exact mode of action in the relief of gout is not completely understood, colchicine is known to decrease the inflammatory response to urate crystal deposition by inhibiting migration of leukocytes, to interfere with urate deposition by decreasing lactic acid production by leukocytes, to interfere with kinin formation and to diminish phagocytosis and the subsequent anti-inflammatory response. The anti-inflammatory effect of colchicine is relatively selective for acute gouty arthritis. However, other types of arthritis occasionally respond. It is neither an analgesic nor a uricosuric and will not prevent progression to chronic gouty arthritis. It does have a prophylactic, suppressive effect that helps to reduce the incidence of acute attacks and to relieve the residual pain and mild discomfort that patients with gout occasionally experience. In some instances, non-steroidal anti-inflammatory drugs (NSAIDs) may also be prescribed to relieve pain and inflammation in acute gouty arthritis attacks. Strong painkillers, such as codeine, or corticosteroids may also be prescribed to relieve the pain.

Colchicine is rapidly absorbed from the gastrointestinal tract. Peak concentrations occur in 0.5 to 2 hours. The drug and its metabolites are distributed in leukocytes, kidneys, liver, spleen and the intestinal tract. Colchicine is metabolized in the liver and excreted primarily in the feces with 10 to 20% eliminated unchanged in the urine.

There remains a need for pure forms of colchicine having low levels of impurities for pharmaceutical use to minimize the potential for side effects in patients taking colchicine pharmaceutical products and to minimize the need for costly toxicity testing required for approval of pharmaceutical products comprising conventional colchicine having high levels of individual or total impurities. In particular, there is a need for stable compositions comprising ultrapure colchicine.

## SUMMARY

Disclosed herein are colchicine compositions.

In one embodiment, the colchicine composition comprises ultrapure colchicine, wherein the ultrapure colchicine comprises no more than about 3.0% total impurities, specifically no more than about 2.0% total impurities, and a pharmaceutically acceptable excipient.

In another embodiment, the colchicine composition comprises ultrapure colchicine, wherein the ultrapure colchicine comprises no more than 3.0% total impurities, specifically no more than about 2.0% total impurities, a filler, a binder, and a disintegrant.

In yet another embodiment, the colchicine composition comprises about 0.6 mg A colchicine, about 12 to about 16 mg pregelatinized starch, about 20 to about 24 mg microcrystalline cellulose, about 3.9 to about 4.7 mg sodium starch glycolate, about 0.5 to about 0.7 mg magnesium stearate, and an amount of lactose monohydrate such that the colchicine dosage form has a total weight of about 100 mg.

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In an embodiment, the colchicine composition comprises colchicine; and a pharmaceutically acceptable excipient; wherein the colchicine composition comprises no more than about 3.5% total impurities and no more than 0.42% N-deacetyl-N-formyl colchicine.

In an embodiment, the colchicine composition comprises colchicine; and a pharmaceutically acceptable excipient, wherein the colchicine composition has 0.6 mgA colchicine, wherein a single dose of the 0.6 mgA colchicine composition has enhanced bioavailability as compared to a single dose of a pharmaceutical product comprising 0.5 mg colchicine after potency correction for colchicine.

In an embodiment, the colchicine composition comprises colchicine; and a pharmaceutically acceptable excipient, wherein the colchicine composition has equivalent bioavailability when administered in a fed or a fasted state.

In an embodiment, the colchicine composition comprises colchicine; and a pharmaceutically acceptable excipient, wherein administration of a single dose of the colchicine composition to a human provides a C<sub>max</sub> between about 1.3 ng/mL and about 4.0 ng/mL, an AUC<sub>0-t</sub> between about 4.4 ng-hr/mL and about 30.8 ng-hr/mL, or an AUC<sub>0-INF</sub> between about 6.7 ng-hr/mL and about 27.8 ng-hr/mL.

Methods of making the colchicine compositions are also disclosed herein.

In an embodiment, the method comprises wet granulating ultrapure colchicine, wherein the ultrapure colchicine comprises no more than about 3.0% of total impurities, with a pharmaceutically acceptable excipient to obtain wet granules, and mixing the granules with a disintegrant to obtain the composition.

In yet another embodiment, the method comprises wet granulating colchicine with a pharmaceutically acceptable excipient to obtain wet granules; drying the wet granules to obtain dried granules; milling the dried granules to obtain milled granules; mixing the milled granules with a disintegrant to obtain the composition; mixing the composition with a lubricant to obtain a tableting blend; and compressing the tableting blend to obtain a colchicine tablet.

Also disclosed herein are methods of making ultrapure colchicine.

In an embodiment, the method comprises subjecting colchicine comprising more than about 3.0% total impurities to column chromatography to obtain a colchicine concentrate, distilling the colchicine concentrate to obtain a colchicine distillate, and crystallizing ultrapure colchicine from the colchicine distillate; wherein the ultrapure colchicine comprises no more than about 3.0% total impurities.

In another embodiment, the method comprises subjecting colchicine comprising more than about 3.0% total impurities to neutral alumina column chromatography to obtain a colchicine concentrate; distilling the colchicine concentrate with ethyl acetate to obtain a colchicine distillate; and crystallizing ultrapure colchicine from the colchicine distillate in ethyl acetate; wherein the ultrapure colchicine comprises no more than about 3.0% total impurities.

In still another embodiment, the method comprises subjecting colchicine comprising more than about 3.0% total impurities to neutral alumina column chromatography to obtain a colchicine concentrate; distilling the colchicine concentrate with ethyl acetate to obtain a colchicine distillate; crystallizing a purified colchicine from the colchicine distillate in ethyl acetate; washing the purified colchicine with ethyl acetate to obtain a washed purified colchicine; and drying the washed purified colchicine to obtain ultrapure colchicine, wherein the ultrapure colchicine comprises no more than about 3.0% total impurities.

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Also disclosed are methods of treating a patient with the colchicine compositions.

In an embodiment, the method comprises administering a dosing regimen to a patient having an acute gouty arthritis attack, wherein the dosing regimen consists of two colchicine dosage forms at the onset of the acute gouty arthritis attack, followed by one colchicine dosage form in about one hour, wherein a colchicine dosage form comprises about 0.6 mgA colchicine.

In an embodiment, the method comprises administering less than about 2 mg of colchicine to a patient over a period of about one hour, wherein the patient is experiencing an acute gouty arthritis attack.

In an embodiment, the method comprises administering to a human experiencing an acute gouty arthritis attack a colchicine composition, wherein the composition is effective to provide a colchicine plasma concentration profile having an area under the plasma colchicine concentration curve from time 0 to infinity (AUC<sub>0-INF</sub>) of about 34.2 ng-hr/mL to about 74.1 ng-hr/mL, an area under the plasma colchicine concentration curve from time 0 to time t (AUC<sub>0-t</sub>) of about 28.8 ng-hr/mL to about 58.9 ng-hr/mL, or a maximum plasma colchicine concentration (C<sub>max</sub>) of about 3.2 ng/mL to about 11.4 ng/mL for a maximum total dose of about 1.8 mg colchicine.

In an embodiment, the method comprises administering a dosing regimen to a patient having an acute gouty arthritis attack, wherein the dosing regimen consists of two colchicine dosage forms at the onset of the acute gouty arthritis attack, followed by one colchicine dosage form in about one hour, wherein a colchicine dosage form comprises about 0.6 mgA colchicine, wherein the dosing regimen is effective to provide an area under the plasma colchicine concentration curve from time 0 to infinity (AUC<sub>0-INF</sub>) of about 34.2 ng-hr/mL to about 74.1 ng-hr/mL, an area under the plasma colchicine concentration curve from time 0 to time t (AUC<sub>0-t</sub>) of about 28.8 ng-hr/mL to about 58.9 ng-hr/mL, or a maximum plasma colchicine concentration (C<sub>max</sub>) of about 3.2 ng/mL to about 11.4 ng/mL.

In an embodiment, the method comprises administering a dosing regimen to a patient having an acute gouty arthritis attack, wherein the dosing regimen consists of two colchicine dosage forms at the onset of the acute gouty arthritis attack, followed by one colchicine dosage form in about one hour, wherein a colchicine dosage form comprises about 0.6 mgA colchicine, wherein the dosing regimen is effective to provide a colchicine plasma concentration profile which has a maximum plasma colchicine concentration (C<sub>max</sub>) which is at least 80% of plasma C<sub>max</sub> provided by a dosing regimen of two dosage forms, followed by one dosage form about every hour later for 6 hours.

In an embodiment, the method comprises administering a dosing regimen to a patient having an acute gouty arthritis attack, wherein the dosing regimen consists of two colchicine dosage forms at the onset of the acute gouty arthritis attack, followed by one colchicine dosage form in about one hour, wherein a colchicine dosage form comprises about 0.6 mgA colchicine, wherein the odds of a patient being a responder to the dosing regimen are not statistically different from the odds of being a responder to a second dosing regimen consisting of two colchicine dosage forms at the onset of the acute gouty arthritis attack, followed by one colchicine dosage form every hour for 6 hours, wherein a responder is a patient obtaining a  $\geq 50\%$  improvement in pain at 24 hours after the first dose, without taking an additional active agent for reducing pain of the acute gouty arthritis attack.

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In an embodiment, the method comprises administering a dosing regimen to a patient having an acute gouty arthritis attack, wherein the dosing regimen consists of two colchicine dosage forms at the onset of the acute gouty arthritis attack, followed by one colchicine dosage form in about one hour, wherein a colchicine dosage form comprises about 0.6 mg. A colchicine, wherein in a randomized, placebo-controlled study of the dosing regimen in patients with an acute gouty arthritis attack, the fraction of patients that experienced a given % improvement in pain at 24 hrs after first dose is shown in FIG. 1.

These and other embodiments, advantages and features of the present invention become clear when detailed description and examples are provided in subsequent sections.

## BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows the fraction of all patients improved at 24 hrs post-first dose of colchicine, regardless of pain rescue, as a function of the percent improvement in pain determined in the study of Example 3.

## DETAILED DESCRIPTION

Disclosed herein are compositions comprising ultrapure colchicine and a pharmaceutically acceptable excipient. Herein, "ultrapure colchicine" means colchicine comprising no more than about 3.0% of total impurities, measured chromatographically as described below, specifically the ultrapure colchicine comprises no more than about 2.0% of total impurities, more specifically no more than about 1.0% of total impurities, or even more specifically no more than about 0.5% of total impurities. In some embodiments, the ultrapure colchicine comprises no more than about 0.10% of N-deacetyl-N-formyl colchicine, measured chromatographically. In some embodiments, the ultrapure colchicine is purified from a botanical source. Methods of making ultrapure colchicine and the compositions comprising the ultrapure colchicine, methods of treating various conditions using the compositions. Dosing regimens are also disclosed.

Not wishing to be bound by theory, it is postulated that the properties of colchicine as an antimitotic agent (e.g. its tubulin binding properties) or its effects on Pgp transporter properties provide the therapeutic effects of colchicine described herein. The methods described herein therefore also contemplate the use of an antimitotic agent with at least one pharmaceutically acceptable excipient. An antimitotic agent can be a drug that prevents or inhibits mitosis, or cell division.

In the specification and claims that follow, references will be made to a number of terms which shall be defined to have the following meaning.

The terms "a" and "an" do not denote a limitation of quantity, but rather denote the presence of at least one of the referenced item. The term "or" means "and/or". The terms "comprising", "having", "including", and "containing" are to be construed as open-ended terms (i.e., meaning "including, but not limited to") unless otherwise noted.

An "active agent" means a compound (including for example, colchicine), element, or mixture that when administered to a patient, alone or in combination with another compound, element, or mixture, confers, directly or indirectly, a physiological effect on the patient. The indirect physiological effect may occur via a metabolite or other indirect mechanism. When the active agent is a compound, then salts, solvates (including hydrates), and co-crystals of the free compound or salt, crystalline forms, non-crystalline forms, and any polymorphs of the compound are contemplated

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herein. Compounds may contain one or more asymmetric elements such as stereogenic centers, stereogenic axes and the like, e.g., asymmetric carbon atoms, so that the compounds can exist in different stereoisomeric forms. These compounds can be, for example, racemates or optically active forms. For compounds with two or more asymmetric elements, these compounds can additionally be mixtures of diastereomers. For compounds having asymmetric centers, all optical isomers in pure form and mixtures thereof are encompassed. In addition, compounds with carbon-carbon double bonds may occur in Z- and E-forms, with all isomeric forms of the compounds. In these situations, the single enantiomers, i.e., optically active forms can be obtained by asymmetric synthesis, synthesis from optically pure precursors, or by resolution of the racemates. Resolution of the racemates can also be accomplished, for example, by conventional methods such as crystallization in the presence of a resolving agent, or chromatography, using, for example, a chiral HPLC column. All forms are contemplated herein regardless of the methods used to obtain them.

"Bioavailability" means the extent or rate at which an active agent is absorbed into a living system or is made available at the site of physiological activity. For active agents that are intended to be absorbed into the bloodstream, bioavailability data for a given formulation may provide an estimate of the relative fraction of the administered dose that is absorbed into the systemic circulation. "Bioavailability" can be characterized by one or more pharmacokinetic parameters.

"Bioequivalence" or "equivalent bioavailability" means the absence of a significant difference in the rate or extent to which the active agent in pharmaceutical equivalents or pharmaceutical alternatives is absorbed into a living system or is made available at the site of physiological activity or the absence of a significant difference in the rate or extent to which the active agent in a pharmaceutical composition is absorbed into a living system or is made available at the site of physiological activity when administered by two different methods (e.g., dosing under non-fasted versus fasted conditions). Bioequivalence can be determined by comparing in vitro dissolution testing data for two dosage forms or two dosing conditions or by comparing pharmacokinetic parameters for two dosage forms or two dosing conditions.

In some embodiments, two products (e.g. an inventive composition and COL-PROBENECID®) or two methods (e.g., dosing under fed (non-fasted) versus fasted conditions) are bioequivalent if the ratio of the geometric mean of logarithmic transformed  $AUC_{0-\infty}$ ,  $AUC_{0-t}$ , or  $C_{max}$  for the two products or two methods is about 0.80 to about 1.25; specifically if the 90% Confidence Interval (CI) limit for the ratio of the geometric mean of logarithmic transformed  $AUC_{0-\infty}$ ,  $AUC_{0-t}$ , or  $C_{max}$  for the two products or two methods is about 0.80 to about 1.25; more specifically if the ratios of the geometric mean of logarithmic transformed  $AUC_{0-\infty}$ ,  $AUC_{0-t}$ , and  $C_{max}$  for the two products or two methods are about 0.80 to about 1.25; yet more specifically if the 90% Confidence Interval (CI) limits for the ratios of the geometric mean of logarithmic transformed  $AUC_{0-\infty}$ ,  $AUC_{0-t}$ , and  $C_{max}$  for the two products or two methods are about 0.80 to about 1.25.

"Colchicine therapy" refers to medical treatment of a symptom, disorder, or condition by administration of colchicine. Colchicine therapy can be considered optimal when effective plasma levels are reached when required. In addition, peak plasma values ( $C_{max}$ ) should be as low as possible so as to reduce the incidence and severity of possible side effects.

"Conventional colchicine" means colchicine comprising more than 3% but no more than about 5.0% total impurities,

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measured chromatographically as described below, and comprising more than about 0.10% of N-deacetyl-N-formyl colchicine.

A “dosage form” means a unit of administration of an active agent. Examples of dosage forms include tablets, capsules, injections, suspensions, liquids, emulsions, creams, ointments, suppositories, inhalable forms, transdermal forms, and the like.

“Dosing regimen” means the dose of an active agent taken at a first time by a patient and the interval (time or symptomatic) at which any subsequent doses of the active agent are taken by the patient. The additional doses of the active agent can be different from the dose taken at the first time.

A “dose” means the measured quantity of an active agent to be taken at one time by a patient.

“Efficacy” means the ability of an active agent administered to a patient to produce a therapeutic effect in the patient.

As used herein, the term “mgA” refers to milligrams of the active colchicine, or the free base of colchicine, after compensating for the potency of the batch of colchicine (i.e., after compensating for impurities, including solvents, and salts in the colchicine). For example, 0.612 mg of an ultrapure colchicine free base having a total impurity of 2 wt % (thus a purity of 98 wt %) contains 0.6 mgA ( $0.612 \text{ mg} \times 0.98 = 0.6 \text{ mgA}$ ) of colchicine.

An “oral dosage form” means a unit dosage form for oral administration.

A “patient” means a human or non-human animal in need of medical treatment. Medical treatment can include treatment of an existing condition, such as a disease or disorder, prophylactic or preventative treatment, or diagnostic treatment. In some embodiments the patient is a human patient.

“Pharmaceutically acceptable” means that which is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes that which is acceptable for veterinary use as well as human pharmaceutical use.

“Pharmaceutically acceptable salts” includes derivatives of colchicine, wherein the colchicine is modified by making acid or base addition salts thereof, and further refers to pharmaceutically acceptable solvates, including hydrates, and co-crystals of such compounds and such salts. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid addition salts of basic residues such as amines; alkali or organic addition salts of acidic residues; and the like, and combinations comprising one or more of the foregoing salts. The pharmaceutically acceptable salts include non-toxic salts and the quaternary ammonium salts of the colchicine. For example, non-toxic acid salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; other acceptable inorganic salts include metal salts such as sodium salt, potassium salt, cesium salt, and the like; and alkaline earth metal salts, such as calcium salt, magnesium salt, and the like, and combinations comprising one or more of the foregoing salts. Pharmaceutically acceptable organic salts includes salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pantoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, mesylic, esylic, besylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic,  $\text{HOOC}-(\text{CH}_2)_n-\text{COOH}$  where n is 0-4, and the like; organic amine salts such as triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, and the like; and amino acid salts such as arginate, asparaginate, glutamate, and the like; and combinations comprising

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one or more of the foregoing salts; organic amine salts such as triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, and the like; and amino acid salts such as arginate, asparaginate, glutamate, and the like; and combinations comprising one or more of the foregoing salts. All forms of such derivatives of colchicine are contemplated herein, including all crystalline, amorphous, and polymorph forms. Specific colchicine salts include colchicine hydrochloride, colchicine dihydrochloride, and co-crystals, hydrates or solvates thereof.

“Pharmacokinetic parameters” describe the in vivo characteristics of an active agent (or a metabolite or a surrogate marker for the active agent) over time, such as plasma concentration (C),  $C_{max}$ ,  $C_n$ ,  $C_{24}$ ,  $T_{max}$ , and AUC. “ $C_{max}$ ” is the measured plasma concentration of the active agent at the point of maximum, or peak, concentration. “ $C_{min}$ ” is the measured plasma concentration of the active agent at the point of minimum concentration. “ $C_n$ ” is the measured plasma concentration of the active agent at about n hours after administration. “ $C_{24}$ ” is the measured plasma concentration of the active agent at about 24 hours after administration. The term “ $T_{max}$ ” refers to the time at which the measured plasma concentration of the active agent is the highest after administration of the active agent. “AUC” is the area under the curve of a graph of the measured plasma concentration of an active agent vs. time, measured from one time point to another time point. For example  $\text{AUC}_{0-t}$  is the area under the curve of plasma concentration versus time from time 0 to time t, where t can be the last time point with measurable plasma concentration for an individual formulation. The  $\text{AUC}_{0-\infty}$  or  $\text{AUC}_{0-\text{INF}}$  is the calculated area under the curve of plasma concentration versus time from time 0 to time infinity. In steady-state studies,  $\text{AUC}_{0-\tau}$  is the area under the curve of plasma concentration over the dosing interval (i.e., from time 0 to time  $\tau$  (tau), where tau is the length of the dosing interval). Other pharmacokinetic parameters are the parameter  $K_e$  or  $K_{el}$ , the terminal elimination rate constant calculated from a semi-log plot of the plasma concentration versus time curve;  $t_{1/2}$  the terminal elimination half-life, calculated as  $0.693/K_{el}$ ;  $\text{CL}/F$  denotes the apparent total body clearance after administration, calculated as  $\text{Total Dose}/\text{Total AUC}_{\infty}$ ; and  $V_{\text{area}}/F$  denotes the apparent total volume of distribution after administration, calculated as  $\text{Total Dose}/(\text{Total AUC}_{\infty} \times K_{el})$ .

“Adverse event” means any untoward medical occurrence in a patient administered an active agent and which does not necessarily have to have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of the active agent, whether or not considered related to the active agent.

“Side effect” means a secondary effect resulting from taking an active agent. The secondary effect can be a negative (unfavorable) effect (i.e., an adverse side effect) or a positive (favorable) effect.

The most frequently reported adverse side effects to colchicine therapy are gastrointestinal, specifically diarrhea; abdominal pain with cramps; nausea; and vomiting. Less frequently or rarely reported adverse side effects associated with colchicine therapy include anorexia, agranulocytosis, allergic dermatitis, allergic reactions, alopecia, angioedema, aplastic anemia, bone marrow depression, myopathy, neuropathy, skin rash, thrombocytopenic disorder, and urticaria.

Determining that a patient experiences an adverse side effect can be performed by obtaining information from the patient regarding onset of certain symptoms which may be

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indicative of the adverse side effect, results of diagnostic tests indicative of the adverse side effect, and the like.

Ultrapure colchicine comprising low levels of individual impurities or total impurities is highly desirable as compared to conventionally available forms of colchicine. Currently, commercially available forms of colchicine often comprise high levels of impurities. Depending on the source or the preparation process, colchicine may comprise some or all of the common impurities shown in Table 1.

TABLE 1

Common Impurities	Chemical Name	Other common name
Impurity A	N-[(7S,12aS)-1,2,3,10-tetramethoxy-9-oxo-5,6,7,9-tetrahydrobenzo[a]heptalen-7-yl]formamide	N-deacetyl-N-formyl colchicine
Impurity B	(-)-N-[(7S,12aR)-1,2,3,10-tetramethoxy-9-oxo-5,6,7,9-tetrahydrobenzo[a]heptalen-7-yl]-acetamide	Conformational isomer
Impurity C	N-[(7S,7bR,10aS)-1,2,3,9-tetramethoxy-8-oxo-5,6,7,8,10a-hexahydrobenzo[a]cyclopenta[3,4]cyclobuta[1,2-c]cyclohepten-7-yl]-acetamide	$\beta$ -Lumicolchicine
Impurity D	N-[(7S,12aS)-3-( $\beta$ -D-glucopyranosyloxy)-1,2,10-trimethoxy-9-oxo-5,6,7,9-tetrahydrobenzo[a]heptalen-7-yl]-acetamide	Colchicoside
Impurity E	N-[(7S,12aS)-3-hydroxy-1,2,10-trimethoxy-9-oxo-5,6,7,9-tetrahydrobenzo[a]heptalen-7-yl]-acetamide	3-O-demethyl colchicine
Impurity F	N-[7S,12aS)-10-hydroxy-1,2,3-trimethoxy-9-oxo-5,6,7,9-tetrahydrobenzo[a]heptalen-7-yl]acetamide	Colchicine

In addition to the common impurities listed above, colchicine may also comprise N-[(7S,12aS)-2-hydroxy-1,3,10-trimethoxy-9-oxo-5,6,7,9-tetrahydrobenzo[a]heptalen-7-yl]-acetamide (“2-O-demethyl colchicine”) impurity. Some analytical methods cannot differentiate 2-O-demethyl colchicine from 3-O-demethyl colchicine.

In addition to the common impurities listed above, colchicine may also comprise other structurally unidentified impurities. In fact, conventional forms of colchicine may comprise as much as 5% of total impurities, determined chromatographically as described below. Such high levels of impurities in conventional colchicine pose several problems. The impurities may cause side effects in patients taking dosage forms comprising conventional colchicine. For example, N-deacetyl-N-formyl-colchicine (Impurity A, also known as Gloriosine) is tumorigenic and has been studied as an anticancer agent. Therefore reduction in the level of N-deacetyl-N-formyl colchicine found in convention colchicine is highly desirable. Additionally, high levels of impurities can also pose a regulatory challenge for pharmaceutical companies using conventional colchicine in products. For a pharmaceutical product comprising an active agent, the United States Food and Drug Administration (FDA) requires “qualification” or toxicity information for any impurity that is greater than the International Conference on Harmonization (ICH) qualification threshold of 0.15% per individual impurity in the active agent substance or 1.0% in the dosage form. Thus, there is a regulatory benefit for a pharmaceutical company to market pharmaceutical products comprising active agents comprising low levels of individual impurities or total impurities in the active agent substance as well as in the dosage form. As a result, for a pharmaceutical composition comprising colchicine, it is in the best interest of both the pharmaceutical company and the patient that impurities be minimized, if possible, in the colchicine and in colchicine compositions or dosage forms.

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The ultrapure colchicine disclosed herein comprises no more than (NMT) about 3.0%; specifically NMT about 2.0%, or more specifically, NMT about 1.0%, or even more specifically NMT about 0.5% of total impurities. In one embodiment, “total impurities” includes the common impurities, Impurities A through F, as well as all structurally unidentified impurities eluting within 1.5 times the retention time of colchicine using an HPLC method as described in more detail below. In another embodiment, other HPLC and HPLC meth-

ods, for example, as described in more detail below, can be used to quantify the level of total impurities.

The ultrapure colchicine may also comprise low levels of individual impurities. In one embodiment, the ultrapure colchicine comprises NMT about 2.0%, specifically NMT about 1.5%; more specifically NMT about 1.0%; or yet more specifically, NMT about 0.5%, or even more specifically, NMT about 0.15%, or still more specifically, NMT about 0.10%, of any individual impurity. The impurity can be Impurity A, Impurity B, Impurity C, Impurity D, Impurity E, Impurity F, or an unidentified impurity.

In an embodiment, the ultrapure colchicine comprises no more than (NMT) about 3.0% total impurities and NMT about 0.10% N-deacetyl-N-formyl colchicine.

In another embodiment, the ultrapure colchicine comprises NMT about 3.0% total impurities; NMT about 0.1% per individual impurity of Impurity A, Impurity C, Impurity D, and Impurity E; NMT about 0.15% Impurity F; and NMT about 2.0% of Impurity B.

Not wishing to be bound by theory, it is postulated that the conformational isomer, Impurity B, is in equilibrium with the active colchicine such that even after purification of the colchicine to about 0.5% Impurity B, the purified colchicine re-equilibrates to a level of Impurity B around about 1% to about 1.3%.

The level of an individual impurity or of total impurities in colchicine may be determined by any suitable analytical method known in the art. In one embodiment, the impurity levels are determined using a high performance liquid chromatography (HPLC) assay, for example, the HPLC method described in the Colchicine Official Monograph USP30/NF25, herein fully incorporated by reference.

Exemplary conditions for HPLC or ultra performance liquid chromatography (HPLC) assays that can be used for the impurity analysis of colchicine or of a colchicine pharmaceutical product are listed in Table 2.

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TABLE 2

Exemplary HPLC Conditions For Colchicine Purity Analysis			
	USP30/NF25 Colchicine Official Monograph Method	HPLC Method	UPLC Method
Mobile phase	0.5 Molar $\text{KH}_2\text{PO}_4$ in Methanol:Water (65:45, v:v), pH adjusted to 5.5 with $\text{H}_3\text{PO}_4$	pH 7.2 10 mM Phosphate Buffer:methanol (MeOH) Gradient	pH 4.5 Ammonium Acetate Buffer:MeOH Gradient
Column	Octylsilyl silica gel, 4.6 mm $\times$ 25 cm, 5 micron	Zorbax SBC(18) 4.6 $\times$ 250 mm	Acquity GEH C18 2.1 $\times$ 100 mm, 1.7 $\mu\text{m}$
Flow rate	1.0 mL/min	1.0 mL/min	0.25 mL/min
Column Temp	Ambient	Ambient	30 C. $\pm$ 2 C.
Detection	254 nanometers (nm)	246 nm	246 nm
Injection volume	20 microliters ( $\mu\text{L}$ )	75 $\mu\text{L}$	7 $\mu\text{L}$
Sample Conc.	0.006 mg/mL	0.120 mg/ml	0.012 mg/ml
Run time	15 minutes (min)	46 min	25 min

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When using one of the above HPLC conditions in Table 2<sup>20</sup> for colchicine purity analysis, the relative retention time (RRT) of an impurity can be calculated by the following formula:

$$\text{RRT of an impurity} = \text{RT of the impurity} / \text{RT of colchicine},$$

where RT stands for retention time of the impurity or the colchicine at the particular conditions used in the assay.

In one embodiment, using the HPLC method in Table 2, the retention time (RT) of colchicine is about 7 minutes and the relative retention times (RRTs) of the common impurities eluting within 1.5 times the retention time for colchicine are listed in Table 2A:

TABLE 2A

Relative Retention Times (RRTs) of the Common Impurities	
Impurity ID	RRT
N-deacetyl-N-formyl colchicine - Impurity A	0.94
Conformational isomer - Impurity B	0.8
$\beta$ -Lumicolchicine - Impurity C	1.2
Colchicoside - Impurity D	0.4
3-O-demethyl colchicine - Impurity E	0.7

In one embodiment, the percent of a particular impurity is calculated by dividing the response (peak area) of the impurity peak by the sum of all responses (total peak area of all peaks, including the colchicine peak and all common and unidentified impurity peaks) eluting within 1.5 times the retention time for colchicine in the HPLC assay and multiplying the result by 100%.

In one embodiment, the level (%) of total impurities is calculated by dividing the sum of responses of any peaks other than that due to colchicine eluting within 1.5 times the retention time for colchicine by the sum of all responses eluting in the HPLC assay and multiplying the result by 100%.

An additional HPLC method for determining the level of impurities other than Impurity F in colchicine or in colchicine pharmaceutical products has been developed and validated for use as an alternative to the methods in Table 2 above. The method is shown in Table 3A below.

TABLE 3A

Quantitative HPLC Method for determining all impurities other than impurity F in colchicine and colchicine pharmaceutical products.	
Quantitative HPLC Method for colchicine and colchicine products.	
Mobile phase	pH 4.5 Ammonium Acetate Buffer:methanol Gradient
Column	Waters XBridge C18, 250 mm $\times$ 4.6 mm, 5 $\mu\text{m}$ particle size
Flow rate	0.9 mL/min
Column Temp	10 $\pm$ 3.5 C. (for column)/10 $\pm$ 2 C. (for sample)
Detection	246 nm
Injection volume	75 $\mu\text{L}$
Sample Conc.	0.16 mg/ml
Run time	60 min

In the quantitative HPLC method of Table 3A, the retention time (RT) of colchicine is about 24 minutes and the relative retention times (RRTs) of the common impurities for colchicine are listed in Table 3B:

TABLE 3B

Relative Retention Times (RRTs) of the Common Impurities	
Impurity ID	RRT
N-deacetyl-N-formyl colchicine - Impurity A	0.93
Conformational isomer - Impurity B	0.82
$\beta$ -Lumicolchicine - Impurity C	1.76
Colchicoside - Impurity D	0.18
3-O-demethyl colchicine - Impurity E	0.52
2-O-demethyl colchicine	0.54
Gamma-Lumicolchicine	1.37

The percentage of individual impurities in the sample solution is calculated as follows:

$$\% \text{ Impurity} = \frac{r_i}{r_s} \times \frac{W_s(\text{mg})}{100 \text{ mL}} \times \frac{6.0 \text{ mL}}{100 \text{ mL}} \times \frac{2.0 \text{ mL}}{100 \text{ mL}} \times P \times \left( \frac{100 - \% RS_s - \% W_s}{100} \right) \times \frac{200 \text{ mL}}{SW(\text{mg}) \times \left( \frac{100 - \% RS_u - \% W_u}{100} \right)} \times \frac{100 \%}{RRF}$$

Where:

$r_s$  = The area response of the Colchicine peak in the Working Standard Solution.

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$r_i$ =The area response of the impurity peak in the Sample Solution

P=% Purity of the Colchicine Reference Standard divided by 100%.

SW=Weight of Sample taken for Sample Preparation

$W_s$ =Weight of Colchicine in the Stock Standard Solution

RRF=Relative Response Factor for specified and unspecified impurities, 1.0

%  $RS_{s/u}$ =Percent of Residual Solvents in the Colchicine Standard/Sample

%  $W_{s/u}$ =% Water in the Colchicine Standard/Sample

To date, the impurity colchicine (Impurity F or 10-O-Demethyl Colchicine "10-DMC") has been typically analyzed by a qualitative colorimetric test described in the Colchicine Official Monograph USP30/NF25 using ferric chloride solution, rather than chromatographically. The standard for acceptable levels of Impurity F has been absence of production of a definite green color in a solution of colchicine.

However, a chromatographic method has been developed for the determination of Impurity F (Colchicine or 10-O-Demethyl Colchicine "10-DMC"). The chromatographic conditions are as follows:

TABLE 3C

HPLC parameters for Colchicine determination	
HPLC System:	HPLC equipped with a pump, auto sampler, variable wavelength detector and a suitable data acquisition system.
Column:	Phenomenex Gemini C18 150 mm × 4.6 mm 5 μm, 110 Å
Detection:	245 nm
Flow Rate:	About 1.5 mL/min
Injection Volume:	50 μL
Temperature:	Column: 10° C. ± 3.5° C. Sample: 5° C. ± 2° C.
Needle Rinse Setting:	Double
Needle Wash:	Water:Acetonitrile (50:50)
Digital Filter Response:	1.0
Sampling Rate:	5.0
Resolution:	1.2
Mobile Phase:	pH 4.5 Buffer Solution:Acetonitrile (75:25)
Run Time:	About 7 minutes for Standard About 20 minutes for first Blank and Samples

The LQL level for 10-DMC in this method is 0.776304 μg/mL. The amount of 10-DMC expressed in percent of Colchicine is calculated as follows:

$$\% \text{ Purity} = \frac{r_i}{r_s} \times \frac{W_s(\text{mg}) \times P}{4000 \text{ mL}} \times \left( \frac{100 - \% RS_s - \% W_s}{100} \right) \times \frac{3.0 \text{ mL}}{100 \text{ mL}} \times \frac{50 \text{ mL}}{W_u(\text{mg}) \times \left( \frac{100 - \% RS_u - \% W_u}{100} \right)} \times \frac{100\%}{RRF}$$

Where:

$r_i$ =The peak area response of 10-DMC in the Sample Solution

$r_s$ =The peak area response of Colchicine in the Working Standard Solution

$W_s$ =The weight of Colchicine in the Stock Standard Preparation

$W_u$ =The weight of Colchicine in the Sample Preparation

P=Standard purity factor expressed as labeled (% Purity/100)

%  $RS_{s/u}$ =Percent of Residual Solvents in the Colchicine Standard/Sample

%  $W_{s/u}$ =% Water in the Colchicine Standard/Sample

RRF=Relative response factor for 10-DMC=0.88

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Ultrapure colchicine may be obtained by various purification methods starting from colchicine-containing botanical extracts, conventional colchicine, or other partially-purified forms of colchicine. In some embodiments, the colchicine is purified from a botanical source. The botanical source can be any capable of providing colchicine, conventional or ultrapure, in quantities suitable for commercial pharmaceutical product manufacture

The literature from 1884-1997 on methods of isolation and purification of colchicine from various botanic sources, including for example *C. autumnale* corms or leaves and species of *Gloriosa* has been reviewed. (Kiselev & Yavich, 1991, "METHODS OF ISOLATING ALKALOIDS OF THE COLCHICINE SERIES"; Plenum Publishing Co., English translation of article from Khimiya Prirodnikh Soedinenii, No. 5, pp. 592-600, September-October, 1990). Kiselev & Yavich also review reports in the literature of impurities detected in colchicine stored for various times, as follows. In an article published in 1944 it was reported that chromatography of colchicine corresponding to the requirements of the USP of that time showed the presence of 5% of impurities and various amount of individual impurities. An article published in 1952 reported that colchicine meeting the requirements of the USP contained about 4% of 3-demethylcolchicine. A 1953 article reported 1.5% of N-formyldeacetylcolchicine isolated and the presence of other accompanying alkaloids in a pharmacopeial sample of colchicine. An investigation of a commercial sample by high-resolution liquid chromatography, published in 1986, reported finding 93.4% of colchicine, 2.9% of N-formyldeacetylcolchicine, 1.8% of 17-hydroxycolchicine, and 0.84% of an unknown substance.

Walaszik et al. describes a process of incorporating carbon 14 into *C. autumnale* plants and isolating radioactive colchicine from the radioactive plants (See Walaszik et al., Science (1952) 116:225-227). However, the level of impurities in the isolated radioactive colchicine is not disclosed.

The purification methods disclosed herein produce ultrapure colchicine comprising very low levels of total impurities or individual impurities. In one embodiment, ultrapure colchicine may be obtained from conventional colchicine obtained commercially or produced using solvent extraction of appropriate botanic material as described in more detail below.

In one embodiment, conventional colchicine may be obtained by isolating colchicine from a colchicine chloroform extract. The extract is washed with a mixture of purified water, sodium hydroxide solution, sodium chloride solution and acetic acid. The washed extract is filtered and the resulting concentrate is distilled in two steps, first using methanol, and second using ethyl acetate. The resulting distillate is crystallized. Ethyl acetate can be used to isolate and wash the crystallized colchicine, which is then dried to yield conventional colchicine. The conventional colchicine comprises more than about 3.0% but no more than 5% total impurities.

The conventional colchicine may be used directly in a colchicine composition comprising a pharmaceutically acceptable excipient. It may also be used for further purification to obtain ultrapure forms of colchicine.

In one embodiment of a method of making ultrapure colchicine, the conventional colchicine may be subjected to column chromatography to obtain a purified colchicine concentrate, distilling the purified colchicine concentrate to obtain a colchicine distillate, and crystallizing ultrapure colchicine from the colchicine distillate. The method can further comprise washing the crystallized ultrapure colchicine with a solvent and drying. The ultrapure colchicine comprises no more than about 3.0% of total impurities.

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In one embodiment, the column chromatography is carried out using methylene chloride as solvent on a column of neutral alumina. Other solvents or chromatographic media may be used, provided that impurities are removed from the conventional colchicine to the desired level. In another embodiment, distillation of the purified colchicine concentrate is carried out using ethyl acetate. Other organic solvents can be used, provided that impurities are removed from the purified colchicine concentrate. In yet another embodiment, the solvent used to wash the crystallized ultrapure colchicine is ethyl acetate.

In another embodiment, a method of making ultrapure colchicine comprises subjecting colchicine comprising more than about 3.0% total impurities to neutral alumina column chromatography to obtain a colchicine concentrate; distilling the colchicine concentrate with ethyl acetate to obtain a colchicine distillate; crystallizing a purified colchicine from the colchicine distillate in ethyl acetate; washing the purified colchicine with ethyl acetate to obtain a washed purified colchicine; and drying the washed purified colchicine to obtain ultrapure colchicine, wherein the ultrapure colchicine comprises no more than about 3.0% total impurities.

In one embodiment, the ultrapure colchicine obtained in any of the above methods comprises no more than about 2.0% total impurities. In another embodiment, the ultrapure colchicine comprises no more than about 1.5% total impurities. In another embodiment, the ultrapure colchicine comprises no more than about 1.0% total impurities. In another embodiment, the ultrapure colchicine comprises no more than about 0.5% total impurities. In yet another embodiment, the ultrapure colchicine comprises no more than about 0.5% per individual impurity of Impurity A, Impurity B, Impurity C, Impurity D, Impurity E, or Impurity F. In still another embodiment, the ultrapure colchicine comprises no more than about 0.15% per individual impurity of Impurity A, Impurity C, Impurity D, Impurity E, or Impurity F. In another embodiment, the ultrapure colchicine comprises no more than about 1.0% of total unidentified impurities. In yet another embodiment, the ultrapure colchicine comprises no more than about 0.5% of total unidentified impurities. In yet another embodiment, the ultrapure colchicine comprises no more than 1.0% of Impurity B, and no more than 0.1% per individual impurity of any of Impurity A, Impurity C, Impurity D, Impurity E, and Impurity F.

The above methods of making ultrapure colchicine are only examples of suitable methods for its preparation.

The colchicine compositions disclosed herein comprise colchicine and a pharmaceutically acceptable excipient. In one embodiment, the colchicine composition comprises 0.1 wt % to 10 wt % colchicine, specifically 0.1 wt % to 5 wt % colchicine. In one embodiment, the colchicine in the colchicine compositions is ultrapure colchicine. The compositions comprising ultrapure colchicine are stable and provide enhanced safety to patients taking the compositions because the patients are ingesting fewer impurities. In particular, the colchicine compositions contain substantially lower levels of the tumorigenic compound N-deacetyl-N-formyl colchicine.

The pharmaceutically acceptable excipient in the colchicine composition may be a filler (or diluent), a binder, a disintegrant, a lubricant, or a combination comprising two or more of the foregoing excipients.

In one embodiment, the pharmaceutically acceptable excipient comprises a filler. Exemplary fillers may be one or more compounds which are capable of providing compactability and good flow. Exemplary fillers include microcrystalline cellulose, starch, lactose, sucrose, glucose, mannitol, maltodextrin, sorbitol, dextrose, silicic acid, dibasic

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calcium phosphate, or a combination comprising at least one of the foregoing fillers. Exemplary lactose forms include lactose monohydrate, NF (Fast Flo), lactose spray-dried monohydrate, and lactose anhydrous. Exemplary microcrystalline cellulose (MCC) include, for example, AVICEL® PH101 and AVICEL® PH102, which are commercially available from FMC Biopolymer, Philadelphia, Pa. Exemplary dibasic calcium phosphates include dihydrated and anhydrous dibasic calcium phosphates. In one embodiment, the filler is a combination of microcrystalline cellulose and lactose monohydrate, NF (fast flo).

When present, the amount of the filler in the composition may be about 10 wt % to about 99 wt %, or more specifically, about 30 wt % to about 90 wt %, or even more specifically, about 50 wt % to about 90 wt %, or still more specifically, about 70 wt % to about 85 wt %, based on the total weight of the composition. In one embodiment, the total amount of the filler is about 82 wt %, based on the total weight of the composition.

In one embodiment, the pharmaceutically acceptable excipient comprises a binder. Binders may be used to impart cohesive qualities to a formulation, for example, a tablet formulation, and thus ensure that the tablet remains intact after compaction. Exemplary binders include starches (for example, Starch 1500® or pregelatinized starch), alginates, gelatin, carboxymethylcellulose, sugars (for example, sucrose, glucose, dextrose, and maltodextrin), polyethylene glycol, waxes, natural and synthetic gums, polyvinylpyrrolidone, and cellulosic polymers (for example, microcrystalline cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methyl cellulose, and hydroxyethyl cellulose) and combinations comprising one or more of the foregoing binders. In one embodiment, the binder is starch, or more specifically, pregelatinized starch.

When present, the amount of the binder may be about 10 wt % to about 99 wt %, or more specifically, about 10 wt % to about 50 wt %, or even more specifically, about 10 wt % to about 20 wt %, based on the total weight of the composition. In one embodiment, the amount of the binder is about 14 wt %, based on the total weight of the composition.

In another embodiment, the pharmaceutically acceptable excipient comprises a disintegrant. Disintegrants are used to facilitate disintegration or "breakup" of a composition, for example, a tablet, after administration. Exemplary disintegrants include sodium starch glycolate, sodium crosscarmellose (cross-linked carboxy methyl cellulose), crosslinked polyvinylpyrrolidone (PVP-XL), anhydrous calcium hydrogen phosphate, agar-agar, potato or tapioca starch, alginic acid, or a combination comprising one or more of the foregoing disintegrants.

When present, the disintegrant may be present in an amount of about 0.1 to 30 wt %, or more specifically, about 1 to 20 wt %, or even more specifically, about 1 to 10 wt %, based on the total weight of the composition. In one embodiment, the amount of the disintegrant is about 4.5 wt %, based on the total weight of the composition.

In another embodiment, the pharmaceutically acceptable excipient comprises a lubricant. Generally, a lubricant is added just before tableting, and is mixed with the rest of the composition for a minimum period of time to obtain good dispersal. Exemplary lubricants include magnesium stearate, calcium stearate, zinc stearate, stearic acid, talc, glyceryl behenate, polyethylene glycol, polyethylene glycol, polyethylene oxide, sodium lauryl sulfate, magnesium lauryl sulfate, sodium oleate, sodium stearyl fumarate, DL-leucine, colloidal silica, or a combination comprising one or more of the

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foregoing lubricants. In one embodiment, the lubricant is magnesium stearate, calcium stearate, or zinc stearate.

When present, the lubricant may be present in an amount of about 0.01 wt % to about 10 wt %, or more specifically, about 0.1 wt % to about 5 wt %, or even more specifically, about 0.1 wt % to about 1 wt %, based on the total weight of the composition. In one embodiment, the amount of the lubricant is about 0.6 wt %, based on the total weight of the composition.

If desired, the composition may optionally comprise small amounts of nontoxic auxiliary substances such as wetting or emulsifying agents, or pH buffering agents, for example, sodium acetate, sorbitan monolaurate, triethanolamine sodium acetate, triethanolamine oleate, sodium lauryl sulfate, dioctyl sodium sulfosuccinate, and polyoxyethylene sorbitan fatty acid esters.

In one embodiment, a composition comprises an ultrapure colchicine, wherein the ultrapure colchicine comprises no more than 3.0% of total impurities, a filler, a binder, and a disintegrant.

In another embodiment, a colchicine composition comprises about 0.6 mgA colchicine; about 14 mg pregelatinized starch; about 22 mg microcrystalline cellulose; about 4.3 mg sodium starch glycolate; about 0.6 mg magnesium stearate; and an amount of lactose monohydrate such that the colchicine composition has a total weight of about 100 mg. In one embodiment, the colchicine in the colchicine composition is ultrapure colchicine.

In an embodiment, a colchicine composition comprises colchicine; and a pharmaceutically acceptable excipient; wherein the colchicine composition comprises no more than about 3.5% total impurities, specifically no more than about 3.0% total impurities, more specifically no more than about 2.0% total impurities, or yet more specifically no more than about 1.0% total impurities. In some of these embodiments, specific limitations on the levels of individual impurities are also met by the colchicine composition. In addition to containing no more than a particular maximum level of total impurities, the colchicine composition can comprise not more than about 0.42% Impurity A, Impurity C, Impurity D, Impurity E, or Impurity F, and not more than about 2.0% Impurity B; specifically not more than about 0.2% Impurity A, Impurity C, Impurity D, Impurity E, or Impurity F, and not more than about 1.5% Impurity B; and more specifically not more than about 0.15% Impurity A, Impurity C, Impurity D, Impurity E, or Impurity F, and not more than about 1.1% Impurity B. In one embodiment the colchicine composition comprises no more than 3.5% total impurities, no more than 0.42% Impurity A, and no more than 2.0% Impurity B. The pharmaceutically acceptable excipient can be one or more discussed previously herein.

In one embodiment, a colchicine composition comprises colchicine and a pharmaceutically acceptable excipient; wherein the colchicine composition comprises no more than about 3.5% total impurities. In some embodiments, the colchicine composition comprises ultrapure colchicine and total impurities in the ultrapure colchicine comprise no more than about 3.0%, or specifically no more than about 2.0%, or more specifically no more than about 1.5%, or yet more specifically, no more than about 1.0%. In addition to containing no more than a particular maximum level of total impurities, the ultrapure colchicine in the colchicine composition can comprise not more than about 0.15% Impurity A, Impurity C, Impurity D, Impurity E, or Impurity F, and not more than about 2.0% Impurity B; specifically not more than about 0.10% Impurity A, Impurity C, Impurity D, or Impurity E; not more than about 0.15% Impurity F, and not more than about

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1.5% Impurity B. In one embodiment the colchicine composition comprises ultrapure colchicine comprising no more than 0.10% Impurity A, no more than about 0.15% Impurity F, and no more than 2.0% Impurity B. The pharmaceutically acceptable excipient can be one or more discussed previously herein.

In one embodiment, a colchicine composition comprises colchicine; a filler; a binder; and a disintegrant; wherein the colchicine composition comprises no more than about 3.5% total impurities. In some embodiments, the colchicine composition comprises ultrapure colchicine and total impurities in the composition comprise no more than about 3.5%, or specifically no more than about 3.0%, more specifically no more than about 2.0%, or yet more specifically, no more than about 1.0%; with individual impurity levels of not more than about 0.42% for Impurity A, Impurity C, Impurity D, Impurity E, or Impurity F, and not more than about 2.0% for Impurity B, or specifically with individual impurity levels of not more than about 0.10% for Impurity A, Impurity C, Impurity D, Impurity E, or Impurity F, and not more than about 2.0% for Impurity B.

In one embodiment, the percent total impurities in the composition is determined in an HPLC assay as described in Colchicine Official Monograph USP30/NF25 as 100% times a sum of responses of any peaks other than that due to colchicine, eluting within 1.5 times the retention time for colchicine, relative to a sum of responses of all peaks eluting within 1.5 times the retention time for colchicine and the percent of an individual impurity in the composition is determined in an HPLC assay as described in Colchicine Official Monograph USP30/NF25 as 100% times the responses of the impurity peak relative to a sum of responses of all peaks eluting within 1.5 times the retention time for colchicine.

In yet another embodiment, the percent total and/or individual impurities in the composition is determined in an HPLC assay or HPLC assay in accordance with the methods described in Table 2 or Table 3A or 3C.

In one embodiment, any of the colchicine compositions described above is in the form of a tablet. As used herein, the term "tablet" means a compressed pharmaceutical dosage form of any shape or size. The tablets described herein may be obtained from the compositions comprising colchicine and a pharmaceutically acceptable excipient. Any of the colchicine compositions can be in the form of any other dosage form known in the art, specifically, any oral dosage form, for example a capsule.

Either wet or dry granulation of a colchicine composition may be used prior to compressing the composition into tablets, or direct compression can be used.

In one embodiment, wet granulation is used to prepare wet granules comprising colchicine. A granulating liquid is used in wet granulation process. Both aqueous and non-aqueous liquids may be used as the granulating liquid. In one embodiment, the granulating liquid is an aqueous liquid, or more specifically, de-ionized water. In an embodiment, the colchicine is ultrapure colchicine.

The amount of the granulating liquid used may depend on many factors, for example, the type of the granulating liquid, the amount of the granulating liquid used, whether a hygroscopic excipient is used, the nature of the active agent, and the active agent loading. In one embodiment, the amount of the granulating liquid is in the range of about 5 wt % to about 50 wt %, or more specifically, about 10 wt % to about 40 wt %, based on the dry weight of the granulating particles prior to wet granulation.

Wet granulation time is generally about 5 to 60 minutes. In one embodiment, the colchicine particles and suitable excipi-

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ents are mixed with the granulating liquid for a period of about 5 to about 45 minutes, or more specifically, about 5 to about 35 minutes. For a small scale, the mixing time is about 1 to about 20 minutes, or more specifically, 3 to 10 minutes. Wet granulation is generally performed at temperatures between about 20° C. to about 35° C., or more specifically, at room temperature (about 25° C.).

Any equipment may be used to contact the granulating liquid with the colchicine and the excipients as long as uniform distribution of the granulating liquid is achieved. For example, small-scale production can be achieved by mixing and wetting the ultrapure colchicine and the excipients in mortars or stainless steel bowls, while for larger quantities, V-blenders with intensifier bars, planetary mixers, rotary granulators, high shear granulators, and fluid-bed granulation equipment may be used. In one embodiment, the granulator is a high shear granulator.

In one embodiment, a method of making a colchicine composition comprises wet granulating colchicine with a pharmaceutically acceptable excipient to obtain wet granules, and mixing the granules with a second excipient to obtain a colchicine composition. In one embodiment, the pharmaceutically acceptable excipient comprises a mixture of a filler and a binder. In another embodiment, the mixture of the filler and the binder comprises pregelatinized starch, lactose monohydrate, and microcrystalline cellulose. In another embodiment, de-ionized water is used as the granulating liquid. In some embodiments, the colchicine is ultrapure colchicine. In an embodiment, the second excipient mixed with the granules is a disintegrant. The colchicine compositions can contain about 0.1 wt % to about 10 wt %, or more specifically, about 0.1 wt % to about 1 wt %, of colchicine, based on the total weight of the colchicine composition.

In an embodiment, the method of making a composition comprises wet granulating colchicine with a pharmaceutically acceptable excipient to obtain wet granules, and mixing the granules with a disintegrant to obtain a colchicine composition. In some embodiments, the method further comprises drying the mixture. In another embodiment, the wet granules are dried to obtain dried granules; and then the dried granules are mixed with a disintegrant to obtain the composition. In another embodiment, the dried granules can be milled to obtain milled granules before mixing the milled dried granules with the disintegrant. In one embodiment, greater than 50% of the milled granules pass through a 45 micron sieve or mesh screen. The method can further comprise mixing the colchicine composition with a lubricant to obtain a tableting blend or compressing the tableting blend to obtain a tablet. The method can further comprise coating the tablet.

In one embodiment, a method of making a colchicine composition comprises wet granulating ultrapure colchicine with a pharmaceutically acceptable excipient to obtain wet granules; drying the wet granules to obtain dried granules; milling the dried granules to obtain milled granules; and mixing the milled granules with a disintegrant to obtain the composition. The ultrapure colchicine can comprise no more than about 3.0% total impurities, with no more than about 0.10% Impurity A, no more than about 0.15% Impurity F, and no more than about 2.0% Impurity B.

In another embodiment, a method of making a colchicine tablet comprises wet granulating colchicine with a pharmaceutically acceptable excipient to obtain wet granules; drying the wet granules to obtain dried granules; milling the dried granules to obtain milled granules; mixing the milled granules with a disintegrant to obtain the composition; mixing the

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composition with a lubricant to obtain a tableting blend; and compressing the tableting blend to obtain a colchicine tablet.

In some embodiments, the wet granules are dried to obtain dried granules before mixing with a second excipient, for example a disintegrant. Wet granules can be dried by any suitable means to remove the granulating liquid and to form dried granules containing colchicine and the pharmaceutically acceptable excipient. The conditions and duration of drying depend on factors such as the liquid used and the weight of the granulating particles. Examples of suitable drying methods include, but are not limited to, tray drying, forced air drying, microwave drying, vacuum drying and fluid bed drying.

The extent of drying may be determined by visual observation and manual manipulation, as is common in the art. The extent of drying may also be determined by sieve analysis, moisture measurements, such as loss on drying (LOD) or other suitable methods. In one embodiment, wet granules are dried until the granules lose less than 5 weight percent (wt %), or more specifically, 3 wt % upon drying at 105° C. based on the total weight of the dried granules prior to drying (or LOD of less than 3 wt %).

After drying, dried granules may be mixed directly with an excipient, for example, a filler, a binder, a disintegrant, or a lubricant, for further processing. Alternatively, dried granules may optionally be subjected to additional processing steps prior to mixing with the excipient. For example, dried granules may be sized to reduce particle size prior to mixing with an excipient. Exemplary sizing operations include milling or sieving. Any suitable equipment for reducing the particle size may be used in the present invention. In one embodiment, the dried granules are milled to obtain milled granules so that at least 50% of the milled granules pass through a 45 micron mesh screen.

Suitable excipients may be added extragranularly and mixed with the granules to form colchicine compositions. As used herein, the term "extragranular" or "extragranularly" means that the referenced material, for example, a suitable excipient, is added or has been added as a dry component after wet granulation. In one embodiment, a disintegrant and a lubricant, in that sequence, are added extragranularly to the granules and mixed to form a blend. The blend may be encapsulated directly into capsule shells, for example, hard gelatin shells, to form capsule formulations. Alternatively, the blend may be compressed into tablets. In some embodiments, the granules are dried granules or milled, dried granules. In some embodiments, the colchicine is ultrapure colchicine.

Mixing can be carried out for a sufficient time to produce homogeneous mixtures or blends. Mixing may be accomplished by blending, stirring, shaking, tumbling, rolling, or by any other method to achieve a homogeneous blend. In some embodiments, the components to be mixed are combined under low shear conditions in a suitable apparatus, such as a V-blender, tote blender, double cone blender or any other apparatus capable of functioning under low shear conditions. The homogenous mixtures or blends are then compressed using any method suitable in the industry.

The colchicine tablets prepared from the above described methods exhibit acceptable physical characteristics including good friability and hardness. The colchicine tablets disclosed herein have friability in the range of about 0% to 3%, specifically about 0 to 1%, more specifically 0% to 0.5%

The colchicine tablet can be coated. Coating the tablet may be performed by any known process. A coating for the colchicine tablet disclosed herein can be any suitable coating, such as, for example, a functional or a non-functional coating, or multiple functional or non-functional coatings. By "func-

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tional coating" is meant to include a coating that modifies the release properties of the total formulation, for example, a sustained-release coating. By "non-functional coating" is meant to include a coating that is not a functional coating, for example, a cosmetic coating. A non-functional coating can have some impact on the release of the active agent due to the initial dissolution, hydration, perforation of the coating, etc., but would not be considered to be a significant deviation from the non-coated composition.

In one embodiment, the tablet is coated with a non-functional coating. The coating can be a white or colored OPADRY® or OPADRY® II (both available from Colorcon, West Point, Pa.), optionally with additional ingredients such as carnauba wax, plasticizers, opacifiers, colorants, and anti-oxidants. In one embodiment, the coating comprises OPADRY® II and carnauba wax.

In an embodiment, a colchicine composition comprises about 0.6 mgA colchicine; about 12 to about 16 mg pregelatinized starch; about 20 to about 24 mg microcrystalline cellulose; about 3.9 to about 4.7 mg sodium starch glycolate; about 0.5 to about 0.7 mg magnesium stearate; and an amount of lactose monohydrate such that the colchicine dosage form has a total weight of about 100 mg. In some embodiments the colchicine composition comprises about 0.6 mgA colchicine, about 14 mg pregelatinized starch, about 22 mg microcrystalline cellulose, about 4.3 mg sodium starch glycolate, about 0.6 mg magnesium stearate, and an amount of lactose monohydrate such that the colchicine dosage form has a total weight of about 100 mg. The colchicine composition can be in the form of a tablet. In some embodiments the tableted composition further comprises a coating comprising Opadry® II and carnauba wax. In an embodiment, the colchicine is ultrapure colchicine.

In one embodiment, a colchicine composition comprising ultrapure colchicine is formulated into an immediate-release formulation. By "immediate-release" is meant a conventional or non-modified release in which greater than or equal to about 75% of the active agent is released within two hours of administration, specifically within one hour of administration.

Active agent release from a pharmaceutical formulation can be analyzed in various ways. One exemplary test is in vitro dissolution. A dissolution profile is a plot of the cumulative amount of active agent released from a formulation as a function of time. A dissolution profile can be measured utilizing the Drug Release Test <724>, which incorporates standard test USP 26 (Test <711>). A profile is characterized by the test conditions selected such as, for example, apparatus type, shaft speed, temperature, volume, and pH of the dissolution medium. More than one dissolution profile may be measured. For example, a first dissolution profile can be measured at a pH level approximating that of the stomach, and a second dissolution profile can be measured at a pH level approximating that of one point in the intestine or several pH levels approximating multiple points in the intestine.

In one embodiment, the immediate-release colchicine composition exhibits a dissolution profile such that at ten minutes after combining the composition with 500 ml of purified water at 37° C. ±0.5° C. according to USP 28 <711> Apparatus 1 (basket), 100 rpm speed, about 90 to about 100 wt. % of the total amount of active agent is released; specifically at 30 minutes after combining the composition with the dissolution medium, about 95 to about 100 wt. % of the total amount of colchicine is released; and more specifically at one hour after combining the composition with the dissolution medium, about 98 to about 100 wt. % of the total amount of colchicine is released.

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Potency, or the amount of active colchicine present in a batch of colchicine, can be determined as described in Colchicine Official Monograph USP 30/NF 25 by comparing an assay sample to a colchicine reference standard (e.g., USP Colchicine RS) sample in the chromatographic assay described in Colchicine Official Monograph USP30/NF25. The quantity of active colchicine in the assay sample, in mg, of C<sub>22</sub>H<sub>25</sub>NO<sub>6</sub> is calculated by the formula:  $10C(r_U/r_S)$ , in which C is the concentration, in µg per mL, of the colchicine reference standard sample; and r<sub>U</sub> and r<sub>S</sub> are the colchicine peak responses obtained from the assay sample and the colchicine reference standard sample, respectively.

In another embodiment, potency of a batch of colchicine can be determined using the HPLC Potency assay described in the table below by comparing an assay sample to a colchicine reference standard.

HPLC Potency Assay B	
Mobile phase	50 mM Potassium Phosphate Buffer:methanol (45:55), pH 5.5 ± 0.05
Column	Phenomenex Luna C8(2), 4.6 mm × 25 cm, 5 µm
Flow rate	1.0 mL/min
Column Temperature	Ambient
Detection	254 nm
Injection volume	20 µL
Sample Conc.	0.120 mg/ml
Run time	15 min

The quantity, in percentage, of C<sub>22</sub>H<sub>25</sub>NO<sub>6</sub> (active colchicine), on an anhydrous, solvent free basis, in the colchicine assay sample is calculated by the formula:

$$\% \text{ Purity} = \frac{r_u}{r_s} \times \frac{W_s(\text{mg}) \times P \times \left( \frac{100 - M_s - S_s}{100} \right)}{500 \text{ ml}} \times \frac{PV(\text{ml})}{VF(\text{ml})} \times \frac{VF_1(\text{ml})}{SW(\text{mg}) \times \left( \frac{100 - M_u - S_u}{100} \right)} \times \frac{VF_2(\text{ml})}{PV_1(\text{ml})} \times 100$$

Where:

r<sub>u</sub>=The peak area of colchicine in the working sample solution

r<sub>s</sub>=The peak area of colchicine in the working standard solution

W<sub>s</sub>=The weight of colchicine in the standard preparation

P=Standard purity factor expressed as labeled % Purity

M<sub>s</sub>=Moisture factor in standard expressed as % Moisture

S<sub>s</sub>=Solvent factor in standard expressed as % Solvent

PV=Pipet volume used for the working standard solution

VF=Volumetric flask used for the working standard solution

SW=Sample weight in the stock sample solution

VF<sub>1</sub>=Volumetric flask used for the stock sample solution

M<sub>u</sub>=Moisture factor in sample expressed as % Moisture

S<sub>u</sub>=Solvent factor in sample expressed as % Solvent

VF<sub>2</sub>=Volumetric flask used for the working sample solution

PV<sub>1</sub>=Pipet volume used for the working sample solution.

Alternatively, potency of a batch of colchicine can be determined by comparing an assay sample to a colchicine reference standard in yet another HPLC assay as follows:

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HPLC Potency Assay C	
HPLC System:	HPLC equipped with a pump, autosampler, variable wavelength detector and a suitable data acquisition system
Column Information:	Phenomenex Gemini C18 150 × 4.6 mm 5 μm 110 Å
Detection:	245 nm
Flow Rate:	1.5 mL/minute
Injection Volume:	20 μL
Column Temperature:	30° C. ± 3° C.
Needle Rinse Setting:	Double
Sampling Rate:	2.0
Resolution:	1.2
Filter Response:	1.0
Digital Filter:	Enabled
Needle Wash/Seal Wash:	Methanol:Water (50:50)
Run Time:	About 15 minutes
Mobile Phase:	pH 6.0 Buffer Solution (50 mM of Potassium phosphate and 4 mM of EDTA):Methanol (60:40)
Diluent:	Water:Methanol (75:25)

The percent purity of Colchicine ( $C_{22}H_{25}NO_6$ ), on an anhydrous, solvent-free basis, is calculated as follows:

$$\% \text{ Assay} = \frac{r_u}{r_s} \times \frac{W_s(\text{mg}) \times P}{50 \text{ mL}} \times \left( \frac{100 - \% RS_s - \% W_s}{100} \right) \times \frac{5.0 \text{ mL}}{100 \text{ mL}} \times \frac{500 \text{ mL}}{W_u(\text{mg}) \times \left( \frac{100 - \% RS_u - \% W_u}{100} \right)} \times 100\%$$

Where:

$r_u$  = The peak area response of Colchicine in the Sample Solution.

$r_s$  = The peak area response of Colchicine in the Working Standard Solution.

$W_s$  = The weight of Colchicine in the Stock Standard Preparation.

$W_u$  = The weight of Colchicine in the Sample Preparation.

P = Standard purity factor expressed as labeled (% Purity/100).

%  $RS_{s/u}$  = Percent of Residual Solvents in the Colchicine Standard/Sample.

%  $W_{s/u}$  = % Water in the Colchicine Standard/Sample.

Disclosed herein are also methods of treatment and dosing regimens.

The compositions comprising ultrapure colchicine disclosed herein may be used to treat or prevent a patient's condition such as acute gouty arthritis, chronic gouty arthritis, acute pericarditis, asthma, Behçet's disease, cancer, chronic gout (prophylaxis), pseudogout cystic disease comprising polycystic kidney disease or cystic fibrosis, demyelinating disease of central or peripheral origin, Dupuytren's contracture, Familial Mediterranean fever, glaucoma, idiopathic pulmonary fibrosis, idiopathic thrombocytopenic purpura, inflammatory disorder comprising rheumatoid arthritis, lentiviral infection, multiple sclerosis, postpericardiotomy syndrome, primary amyloidosis, primary biliary cirrhosis, proliferative vitreoretinopathy, pyoderma gangrenosum, recurrent pericarditis, or a condition in need of enhanced bone formation or bone mineral density.

The traditional dose of colchicine used to treat or prevent an attack of acute gouty arthritis has been about 1.0 to about 1.2 mgA of colchicine, for example, two tablets each comprising about 0.6 mgA colchicine. This dose may be followed by one unit of the composition every hour, or two units every

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two hours, until pain is relieved or until diarrhea ensues ("diarrheal dose"). After the initial dose, it is sometimes sufficient to take about 0.6 mgA colchicine every two or three hours. The dosing should be stopped if there is gastrointestinal discomfort or diarrhea. (Opiates may be needed to control diarrhea.) In subsequent attacks, the patient should be able to judge his medication requirement accurately enough to stop short of his diarrheal dose. The total amount of colchicine needed to control pain and inflammation during an attack has been believed to be in the range from about 4 mgA to about 8 mgA. An interval of three days between colchicine courses is advised in order to minimize the possibility of cumulative toxicity.

In one embodiment, a method of treating acute gouty arthritis comprises administering two colchicine dosage forms each comprising about 0.6 mgA colchicine at the onset of the acute gout attack, followed by one dosage form every hour for m hours, wherein the value of m is 1 to 8. In one embodiment, the value of m is 1 to 6. In another embodiment, the value of m is 1 (total of 3 tablets). In yet another embodiment, the value of m is 6 (total of 8 tablets). The colchicine in the dosage form can be ultrapure colchicine. The dosage form can be any oral dosage form, specifically a tablet.

In another embodiment, a method of treating Familial Mediterranean Fever comprises administering 1/2 dosage form to four dosage forms daily, each dosage form comprising about 0.6 mgA colchicine (total of about 0.3 to about 2.4 mgA colchicine daily). In another embodiment, a method of prophylactically treating chronic gout comprises administering one-half dosage form, one dosage form, two dosage forms, or three dosage forms, each dosage form comprising about 0.6 mgA of colchicine, daily. In another embodiment, a method of treating Behçet's disease comprises administering one dosage form comprising about 0.6 mgA of colchicine twice daily (total of 2 dosage forms). The colchicine in the dosage form can be ultrapure colchicine. The dosage form can be any oral dosage form, specifically a tablet.

In one embodiment, a method of treating patients with some but not all of the symptoms of acute gout, chronic gout (prophylaxis), or pseudogout, where the patients are not clinically or informally diagnosed with one of these diseases, comprises administering one or more of the dosage forms comprising about 0.6 mgA of colchicine. The colchicine in the dosage form can be ultrapure colchicine.

The invention should not be considered limited to these particular conditions for combining the components and it will be understood, based on this disclosure that the advantageous properties can be achieved through other conditions provided the components retain their basic properties and substantial homogeneity of the blended formulation components of the formulation is otherwise achieved without any significant segregation.

The following examples further illustrate the invention but should not be construed as in any way limiting its scope. In particular, the processing conditions are merely exemplary and can be readily varied by one of ordinary skill in the art.

## EXAMPLES

## Example 1

## Exemplary Ultrapure Colchicine

As discussed above, ultrapure colchicine with reduced levels of individual and total impurities was desired by the inventors for formulation into a new dosage form in order to minimize potential adverse reactions from the impurities in

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patients taking the dosage form and to reduce the expense of qualification testing during the approval process for marketing the new dosage form. Batches of conventional colchicine were previously obtained from Sanmar Specialty Chemicals Limited (Berigari, India). Conventional colchicine can be further purified to form ultrapure colchicine meeting the following impurity specifications:

TABLE 4

Purity Specifications for an exemplary batch of Ultrapure Colchicine		
Impurity, Common name	Impurity	NMT %
N-deacetyl-N-formyl colchicine	A	0.10
Conformational isomer	B	1.0
$\beta$ -Lumicolchicine	C	0.10
Colchicoside	D	0.10
3-O-demethyl colchicine	E	0.10
Total Impurities		2.0

Ultrapure colchicine was prepared to meet the purity specifications in Table 4 as described below.

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First, conventional colchicine was obtained from a colchicine chloroform extract. The extract was washed with a mixture of purified water, sodium hydroxide solution, sodium chloride solution and acetic acid. The washed extract was filtered and the resulting concentrate was distilled in two steps, first using methanol, and second using ethyl acetate. The resulting distillate was crystallized. Ethyl acetate was used to isolate and wash the crystallized colchicine, which was then dried, resulting in the conventional colchicine. This process is also referred to herein as the "old process".

Second, the conventional colchicine was then subjected to column chromatography on neutral alumina using methylene chloride as solvent. The resulting concentrate was distilled using ethyl acetate, crystallized, isolated and washed using ethyl acetate, and dried, resulting in ultrapure colchicine. This method of generating conventional colchicine, followed by the additional chromatography purification step is also referred to herein as the "new process".

The impurity levels of the lot of ultrapure colchicine and two lots of conventional colchicine were analyzed using the USP30/NF25 Colchicine Official Monograph HPLC method ("USP method") described in Table 2 above. The impurity levels are shown in Table 5.

TABLE 5

Colchicine Lot	Impurity Level, %			
	N-Deacetyl-N-formyl colchicine - Impurity A	Conformational Isomer - Impurity B	Total Unidentified Impurities	Total Impurities
Ultrapure (RD0600164)	ND*	0.5	ND*	0.5
Conventional-1 (RD060075)	2.1	0.6	ND*	2.7
Conventional 2 (RD060055)	2.2	0.6	ND*	2.8

\*ND—None detected.

Table 5 shows that ultrapure colchicine has fewer impurities than each of the conventional colchicine lots. Total impurities of the Ultrapure Lot using the USP method were about 0.5%. On the other hand, total impurities of conventional Lots #1 and 2 were about 2.7% and 2.6%, respectively.

Determined impurity levels may differ depending on the test method used. Table 5B contrasts the determined levels of the conformational isomer, Impurity A (N-deacetyl-N-formyl colchicine), and total impurities for the three colchicine lots using the three methods described in Table 2. The three methods show a maximum absolute variability in the percent determined of 0.8% for N-deacetyl-N-formyl colchicine, of 0.5% for conformational isomer, and 0.7% for total impurities.

TABLE 5B

Levels of impurities in colchicine lots determined using methods of Table 2.										
Lot name (Lot #)	Purification Process	Conformational Isomer			N-deacetyl-N-formyl colchicine			Total Impurities		
		UPLC Method	HPLC Method	USP Method	UPLC Method	HPLC Method	USP Method	UPLC Method	HPLC Method	USP Method
Conventional-1 (RD060055)	Old	0.9	0.8	0.6	3.0	2.5	2.2		3.5	2.8
Conventional 2 (RD060075)	Old	0.9	0.8	0.6	2.7	2.3	2.1		3.2	2.7
Ultrapure (RD0600164)	New	0.9	1.0	0.5	ND*	ND	ND		1.1	0.5

\*ND, none detected.

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Regardless of the testing method used for measuring these impurity levels, the impurity levels for ultrapure colchicine manufactured using the new process remains below the specifications set forth in Table 4.

The ultrapure colchicine of the present invention was prepared to meet the organic volatile impurity specifications ("residual solvents") in Table 6 as described below. The residual solvents are determined using USP <467> test method. In addition to the known and existing solvents, specifications were also set for residual solvent peaks that were seen in HPLC assay testing as described in Tables 2, 3A, or 3C, which solvents are not expected or previously existing for the residual solvent test methods for colchicine or were not identifiable.

TABLE 6

Specifications for Organic Volatile Impurities	
Organic volatile	NMT
Chloroform	100 ppm
Methanol	3000 ppm
Methylene Chloride	600 ppm
Ethanol	5000 ppm
Ethyl Acetate	6.0%
Ethyl Propionate	5000 ppm
Propyl Acetate	5000 ppm
Others	500 ppm each

## Example 2

## Stable Tablets Comprising Ultrapure Colchicine

Stable colchicine compositions comprising the ultrapure colchicine described in Example 1 were manufactured using the following process. Ultrapure colchicine as described in Example 1 was dissolved in purified water. Pregelatinized starch (Starch® 1500), lactose monohydrate, NF (Fast Flo), and microcrystalline cellulose, NF (Avicel PH101) were placed in a 150-liter high shear granulator and mixed. The aqueous ultrapure colchicine solution was added to the granulator while mixing. The wet granules were dried in an oven at 50° C. until the loss on drying of the material was less than 3 wt %. The dried granules were milled through a Fitzmill equipped with a 1βscreen.

The milled granules were charged into a 5 cubic foot Gemco Double Cone Blender and blended with screened sodium starch glycolate, NF (GLYCOLYS®). Then, screened magnesium stearate, NF was added to the blender. Blending was continued and a final tableting blend was made.

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This final tableting blend was compressed into core tablets. These core tablets were film-coated with OPADRY® II purple and carnauba wax. The composition of the ultrapure colchicine tablets is shown in Table 7.

TABLE 7

Ingredient	Amount Per Tablet, mg
Ultrapure Colchicine	0.6 <sup>1</sup>
Pregelatinized starch, NF (Starch 1500)	14.0
Lactose Monohydrate, NF (Fast Flo)	Varies <sup>2</sup>
Microcrystalline Cellulose, NF (Avicel PH101)	21.6
Sodium Starch Glycolate, NF (GLYCOLYS)	4.3
Magnesium Stearate, NF	0.6
Total core tablet	100
OPADRY II Purple (#40L10039)	4.0
Carnauba Wax	0.01

<sup>1</sup>Colchicine amount is shown in units of mgA, adjusted for purity of the lot of colchicine.

<sup>2</sup>Amount adjusted, depending on the actual amount of the colchicine lot added, to maintain an overall core tablet weight of 100 mg.

As a comparison, the lot of conventional colchicine designated in Example 1 as "conventional-2" was substituted in place of ultrapure colchicine in the same tablet formulation shown in Table 7. The same process of making the tablets as described above was used.

The impurities in the tablet comprising the ultrapure colchicine and that comprising the conventional colchicine were analyzed using the HPLC method described in Table 2 above. The impurity levels of both colchicine tablets are shown in Table 8.

TABLE 8

			Impurity Content, %			
Colchicine Product Lot	Colchicine Lot	Process	N-Deacetyl-N-formyl colchicine (Impurity A)	Conformation Isomer (Impurity B)	Total Unknown Impurities	Total Impurities
A	Ultrapure	New	ND*	1.1	0.1	1.2
B	Conventional-2	Old	2.3	1.2	ND*	3.6

\*ND—None detected.

It can be seen from Table 8 that the tablet comprising the ultrapure colchicine has less total impurities than that comprising the conventional colchicine.

The colchicine composition comprising ultrapure colchicine at 6 month stability time points under conditions of 25° C./60% relative humidity and 40° C./60% relative humidity exhibits impurity content ranges of Not Detected to about 0.1% for Impurity A, less than about 1.0% for total unknown impurities compared to a colchicine composition comprising conventional colchicine which exhibits impurity content of greater than about 1.5 for Impurity A and greater than about 2.0% for total unknown impurities when tested under the same conditions.

Table 9 below provides data on impurity levels and stability of impurity levels of colchicine composition batches manufactured using ultrapure and conventional colchicine, and impurity levels for two lots of commercially available COL-PROBENECID® tablets (Watson Laboratories), an FDA-approved combination dosage form comprising colchicine and probenecid.

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TABLE 9

Material	Lot	Colchicine		Conformational Isomer		N-Deacetyl peak	
		purification Process	Conditions of Stability Study	UPLC Method	HPLC Method	UPLC Method	HPLC Method
COL-PROBENECID ®	L6C0395	N/A	N/A	0.8	—	2.2	—
(Probenecid/Colchicine) Tablets†	L6M1440	N/A	N/A	0.8	—	2.5	—
Colchicine Product Lot	B	Old process	room temp, at release	0.9	1.2	2.8	2.3
			12 mo 25 C./60% RH	0.9	0.9	2.7	2.6
	A	New process	room temp, at release	1.0	1.2	ND	ND
			6 mo 25 C./60% RH	1.0	0.8	ND	ND
			6 mo 40 C./75% RH	1.0	1.1	ND	ND
	C	New process	room temp, at release	1.0	1.1	ND	ND
			6 mo 25 C./60% RH	0.9	0.9	ND	ND
			6 mo 40 C./75% RH	1.0	1.1	ND	ND
	D	New process	room temp, at release	1.0	1.1	ND	ND
			6 mo 25 C./60% RH	1.0	1.0	ND	ND
			6 mo 40 C./75% RH	0.9	1.1	ND	ND

—, not analyzed;

†Commercially available;

N/A, not applicable;

ND, none detected.

For comparison, several lots of an FDA-approved colchicine-probenecid combination dosage form and various unapproved commercial colchicine dosage forms were tested for levels of impurities using the HPLC method of Table 2. Results are shown in the tables below.

Impurities in FDA-Approved Colchicine/Probenecid Combination Product				
Impurity	Watson Laboratories Colchicine/Probenecid Tablets			
	L7G1085	L7G1085	L7G1087	L7E0808
Conformational Isomer	1.0%	1.0%	0.8%	1.0%

-continued

Impurities in FDA-Approved Colchicine/Probenecid Combination Product				
Impurity	Watson Laboratories Colchicine/Probenecid Tablets			
	L7G1085	L7G1085	L7G1087	L7E0808
N-deacetyl-N-formyl colchicine	2.0%	2.0%	1.5%	2.0%
Largest Unknown	0.1%	0.1%	0.1%	0.1%
Total Impurities	3.1%	3.1%	2.4%	3.2%

Impurities in Unapproved Colchicine Products						
Impurity	West-Ward			Vision		
	62303A*	63842A	63843A	C07003	C07049	C07058
Exp Date	Jan-2009	May-2011	May-2011	Jan-2009	Aug-2009	Sep-2009
Conformational Isomer	1.1/0.9%	0.9%	0.9%	1.1/0.8%	0.9%	0.9%
N-deacetyl-N-formyl colchicine	2.5/2.6%	2.0%	1.8%	1.3/1.3%	2.7%	2.6%
Largest Unknown	1.7/1.6%	0.5%	0.3%	0.1/0.1%	0.1%	0.3%
Total Impurities	5.3/5.3%	3.5%	3.1%	2.5/2.3%	3.8%	4.0%
Impurity	Qualitest			Akyma		
	T105G07A	T107G07A	T108G07A	3A5246004*		
Exp Date	Jul-2010	Jul-2010	Aug-2010	Jan-2008		
Conformational Isomer	1.0%	0.9%	0.9%	1.1/0.9%		
N-deacetyl-N-formyl colchicine	%1.4	1.3%	1.3%	1.4/1.5%		
Largest Unknown	0.3%	0.2%	0.2%	0.2/0.1%		
Total Impurities	2.7%	2.7%	2.6%	2.9/2.5%		

\*Values from two separate analyses reported

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Summary of Impurities in Marketed Colchicine Products with Batches of colchicine tablets using ultrapure colchicine			
Impurity	Marketed Colchicine Products		Product Lots with Ultrapure Colchicine
	Minimum	Maximum	Maximum
Conformational Isomer	0.8%	1.1%	1.1%
N-deacetyl-N-formyl colchicine	1.3%	2.7%	ND
Largest Unknown	0.1%	1.7%	0.3%
Total Impurities	2.4%	5.3%	1.4%

ND = none detected

The total impurities found in ultrapure colchicine and colchicine products comprising ultrapure colchicine are significantly lower compared to the approved and unapproved, marketed colchicine products. In addition, the maximum total impurities value observed by testing 14 approved or unapproved marketed products was 5.3%; while the maximum value seen to date in inventive ultrapure colchicine product batches was 1.4%. This represents a 75% reduction in total impurities.

Of particular significance, the level of the known impurity, N-deacetyl-N-formyl-colchicine (Impurity A, also known as Gloriosine) has been reduced from levels exceeding 2% to levels to undetectable levels that comply with the ICH Q3A (R2) qualification threshold of 0.15% for an active agent. Gloriosine is tumorigenic and has been studied as an anti-cancer agent. Purification of conventional colchicine to obtain ultrapure colchicine has effectively reduced all individual impurity levels in the colchicine to substantially reduce exposure of patients to this tumorigenic impurity.

### Example 3

#### Therapeutic Effects of Ultrapure Colchicine Formulation

The therapeutic effect of the ultrapure colchicine formulation containing 0.6 mgA of colchicine obtained in Example 2 is evaluated in a clinical study that is a multicenter, randomized, double-blind, placebo-controlled, parallel group, 1-week, dose comparison study designed to evaluate the efficacy of ultrapure colchicine in treating an acute gout attack (acute gouty arthritic attack) in patients with acute gout. A sufficient number of patients are screened to enroll and randomize 300 patients (100 patients per treatment group) who meet the criteria of the American College of Rheumatology (ACR) for acute arthritis of gout. The primary objective of the study is to demonstrate the efficacy of colchicine in an acute gout attack (gouty flare) based on pain reduction after 24 hours as a measure of response. Secondary objectives of the study are to compare low-dose and standard-dose dosing regimens of colchicine with respect to pain, time to response and complete pain relief, interference with sleep, and signs and symptoms of inflammation and to determine the safety of colchicine when administered in the two different dosing regimens.

#### Description of Study

The study will consist of three distinct phases and the number of visits to the study clinic will vary depending on conditions pertaining to an individual patient's acute gout flare experienced in the study as described below. The Pre-Flare Phase will consist of up to two visits to the study clinic

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(with additional interim visits for clinical laboratory testing every 3 months until acute gout flare onset): Visit 1 (Screening) and Visit 2 (Randomization). The Flare Phase will not include a visit to the study clinic. The Post-Flare Phase will consist of up to three visits to the study clinic: Visit 3 (as soon as possible [ASAP] up to 48 hours post-flare onset; if a patient cannot complete Visit 3 in the first 48 hours post-flare onset, Visit 3 will be waived and the patient should return to the clinic for Visit 4), Visit 4 (>48 to 96 hours post-flare onset in patients who took at least one dose of study drug and in patients who did not qualify for treatment with study drug during the Flare Phase but did not complete Visit 3), and Visit 5 (7 days post-flare onset to be conducted in patients who took at least one dose of study drug and whose acute gout flare was still ongoing at Visit 4). For those patients in whom the acute gout flare is not resolved at Visit 5 (based on the judgment of the Investigator) or in whom there is an unresolved AE or clinically significant treatment-emergent laboratory abnormality, there will be one additional follow-up visit 14 days post-flare onset (Visit 6).

When a patient develops an acute gout flare, the patient will call the trained personnel at the Gout Flare Call Center (available 24 hours/day throughout the duration of the study). The patient will be queried regarding any changes in his/her medical health and concomitant medication use since the time of randomization. In order to establish if the patient's acute gout flare will be eligible for treatment with study drug, a standardized questionnaire will be used to document that the patient has all of the following signs/symptoms of the affected joint(s): swelling, erythema, marked tenderness, and pain. In addition, a patient must have at least one of the following: rapid onset of maximum pain within the prior 4 to 12 hours, decreased range of motion in the joint, warmth, or other symptom similar to a prior gout flare. Patients will be asked to rate the pain severity for each joint affected by the acute gout flare by using a study diary. Patients must have at least one joint affected by an acute gout flare with a pain assessment of  $\geq 4$  on the PI-NRS at the onset of the acute gout flare during the Flare Phase prior to taking study drug. If signs and symptoms of an acute gout flare are confirmed and the gout flare is considered eligible for treatment with study drug, the patient will also be instructed to begin taking study drug and to continue completing the patient diary. Patients will be instructed to stop taking study drug and to call the investigational site if at any time they experience a severe gastrointestinal event while taking study drug. The Gout Flare Call Center will call the patient in 24 hours from the onset of the acute gout flare to ensure that the patient has completed the patient diary, including assessments for pain at 24 hours.

In the event that the Gout Flare Call Center determines that the patient does not qualify for treatment with study drug, the patient may be asked to call back in 1 hour for re-assessment. Patients who do not qualify for treatment with study drug may seek alternative therapy without prejudice to further study participation should another acute gout flare occur.

The Gout Flare Call Center will contact patients on a monthly basis beginning 1 month after randomization to study drug. These contacts will continue until the patient has an acute gout flare or study completion, whichever occurs first. The purpose of these contacts is to re-educate patients about study participation.

#### Post-Flare Phase:

Visit 3: After developing an acute gout flare, whether eligible for treatment with study drug or not, all patients will return to the clinic as soon as possible after acute gout flare onset for clinical assessments. If a patient cannot complete Visit 3 in the first 48 hours post-flare onset, Visit 3 will be

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waived and the patient should return to the clinic for Visit 4. For patients whose acute gout flare was deemed eligible for treatment with study drug and at least one dose of study drug was taken, Investigators will examine the patient and complete clinical assessments, patient diaries will be collected, the patient will be queried for concomitant medication use and Adverse Events (AEs), and the study drug blister pack will be collected. For patients whose acute gout flare was deemed not eligible for treatment with study drug by the Gout Flare Call Center, continued eligibility for the study will be confirmed by the Investigator based on review of the inclusion and exclusion criteria as well as the responses to the standardized questionnaire and examination of the patient. Patient diaries will be collected and patients will be queried for concomitant medication use and AEs.

Visit 4: The second Post-Flare Phase visit is to be conducted >48 to 96 hours following acute gout flare onset. It will take place in patients who took at least one dose of study drug and also in those patients who did not qualify for treatment with study drug during the Flare Phase but did not complete Visit 3. For patients whose acute gout flare was deemed eligible for treatment with study drug and at least one dose of study drug was taken, Investigators will examine the patient and complete clinical assessments, patient diaries will be collected, patients will be queried for concomitant medication use and AEs, and the study drug blister pack will be collected (if not previously collected). Patients who took at least one dose of study drug and whose acute gout flare is still ongoing at Visit 4 will return to the clinic for a final visit (Visit 5) 7 days post-flare onset; however, if their acute gout flare is resolved at Visit 4, final study assessments, including collection of samples for laboratory safety and a complete physical examination, will be performed at Visit 4. For patients whose acute gout flare was deemed not eligible for treatment with study drug by the Gout Flare Call Center who did not have a Visit 3, continued eligibility for the study will be confirmed by the Investigator based on review of the inclusion and exclusion criteria as well as the responses to the standardized questionnaire and examination of the patient. Patient diaries will be collected and patients will be queried for concomitant medication use and AEs.

Visit 5/Early Termination: The final visit for the study will take place 7 days after the acute gout flare onset in patients who took at least one dose of study drug and whose acute gout flare was still ongoing at Visit 4. Patients will be examined and clinical assessments will be made. A complete physical examination will be conducted. Samples for clinical laboratory testing will be collected. Patient diaries will be collected and patients will be queried for concomitant medication use and AEs. The study drug blister pack will be collected (if not previously collected).

Visit 6/Follow-up: For those patients in whom the acute gout flare is not resolved at Visit 5 (based on the judgment of the Investigator) or in whom there is an unresolved AE or clinically significant treatment-emergent laboratory abnormality, there will be one additional follow-up visit 14 days post-flare onset (Visit 6).

For inclusion in the study, a patient must be 18 years of age or older, must present with a confirmed diagnosis of gout consistent with the criteria of the ACR, and must have experienced  $\geq 2$  acute gouty arthritic attacks in the 12 months prior to randomization. Patients on urate-lowering therapy must be on a stable dose and schedule with no changes in therapy for 4 weeks prior to randomization and expected to remain on a stable regimen during study participation.

Patients with acute polyarticular gout (>4 joints); taking colchicine routinely; with a known hypersensitivity to colchi-

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cine; with a history of myocardial infarction, unstable angina, cerebrovascular events, or coronary artery bypass grafting; with active myeloid leukemia, obstructive gastrointestinal cancer, or metastatic cancer; with chronic renal dysfunction, with chronic hepatic dysfunction are excluded from the study. Patients using systemic corticosteroid, cyclosporine, adalimumab, etanercept, infliximab, anakinra, abatacept, mycophenolate, azathioprine, or chronic use of non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, tramadol, and other analgesics such as opiates at screening are also be excluded.

The three treatment groups in this study are two ultrapure colchicine tablets (1.2 mgA) administered at the onset of an acute gout attack followed by one tablet (0.6 mgA) after one hour and one placebo tablet every hour thereafter for 5 hours (the "low" dose regimen); two ultrapure colchicine tablets (1.2 mgA) administered at the onset of an acute gout attack followed by one tablet (0.6 mgA) every hour for six (6) hours (the "standard" dose regimen); or two placebo tablets at the onset of an acute gout attack followed by one placebo capsule every hour thereafter for 6 hours (the "placebo" regimen).

Efficacy assessment will be made based on patient and Investigator inputs. Patients will record pain severity and sleep interference on a study diary. The severity of pain for each joint affected by the acute gouty arthritic attack will be rated on an 11-point pain intensity numerical rating scale (PI-NRS) that ranges from 0 ("no pain") to 10 ("worst possible pain"). Recordings are to be made prior to each dose of study drug, i.e., pre-treatment with study drug and for the first 8 hours following start of treatment, and every 8 hours thereafter (while awake) until symptoms disappear or 72 hours have passed since the first dose of study drug was taken, whichever occurs first. The patient's pain assessment of each affected joint as reported by the patient at pre-treatment with study drug and at 24 hours post-start of study drug will be documented by a central Study Center to be used in the event the patient fails to provide data on his/her study diary for either of these two key time points. In the morning upon awakening, the patient is to rate sleep interference due to the acute gout flare in the study diary on an 11-point scale that ranges from 0 ("pain did not interfere with sleep") to 10 ("pain completely interfered; patient was unable to sleep"). Investigators will provide clinical assessments in the clinic at all Post-Flare Phase study visits, and at medically necessary intervening visits. For these assessments, each of the patient's joints affected by the acute gouty arthritic attack will be examined and signs and symptoms of inflammation will be rated (erythema [absent, present, or not assessable], swelling [0, "none" to 3, "severe"], and tenderness to touch [0, "none" to 3, "severe"]). At the final clinic visit, the Investigator will also provide a global assessment of response to treatment ranging from 0 ("excellent") to 4 ("none").

The primary efficacy variable is response to treatment in the target joint, based on patient self-assessment of pain at 24 hours post-dose. The target joint is identified during data analysis as that joint affected by the acute gout flare with the highest baseline pain score on the patient diary. Ties among maximum joint scores for an individual are resolved by random selection. A responder is one who provides both a pre-treatment and valid 24-hour pain score and achieves a  $\geq 50\%$  reduction in pain score at the 24-hour post-dose assessment relative to the pre-treatment score and does not use rescue medication. Patients who use rescue medication, discontinue prior to the 24-hour post-dose assessment, or do not achieve a  $\geq 50\%$  reduction in pain score at the 24 hour post-dose assessment relative to the pre-treatment score are deemed non-responders.

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The secondary efficacy variables are assessments of magnitude of pain reduction, time to response, time to complete pain relief, and interference with sleep as recorded on patient diaries by the patient. Signs and symptoms of inflammation per Investigator's clinical assessments of the target joint are evaluated. Time to drop out (use of rescue medications) is also evaluated. Investigator global assessment of response to treatment is assessed.

The primary efficacy analysis will be based on an Intent-to-Treat (ITT) population, defined as all patients who were randomized, contacted the Gout Flare Call Center, took at least one dose of study drug, and had one subsequent contact. The Per Protocol (PP) population is defined as the subset of the ITT population confirmed by the Investigator as continuing to meet all major inclusion and exclusion criteria and initiating treatment within hours of the onset of the acute gout flare. Analyses will also be made on an Evaluable patient population with an Evaluable patient defined as one who, in addition to being included in the PP population, completed the randomized treatment course. The ITT population will be used for the evaluation of safety.

Statistical tests for efficacy analysis are two-tailed with an alpha significance level of 0.05.

For primary efficacy analysis, the number of responders in the standard-dose colchicine group and the placebo group, as defined for the primary efficacy variable, will be compared using the Mantel-Haenszel chi-square test stratified on study site. The comparison of the standard-dose colchicine and placebo groups of the ITT population is the primary comparison of interest. The sensitivity to alternate definitions of response (based both on magnitude of reduction from baseline as well as time point) will be evaluated as secondary endpoints. As additional sensitivity analyses, these tests will also be repeated for the PP and Evaluable populations if the sample sizes differ from the overall ITT population by more than 10%.

For secondary efficacy analysis, the number of responders in the low-dose colchicine group will be compared to placebo and also to standard-dose colchicine using the Mantel-Haenszel chi-square test stratified on study site. Change in pain intensity, interference with sleep, time to 50% reduction in pain, and time to complete pain relief will be analyzed as continuous variables using analysis of covariance with study site, treatment group, and site by treatment interaction as independent variables for change in pain intensity and interference with sleep, with baseline score as a covariate. For the Investigator's clinical assessment of inflammation (erythema, swelling, and tenderness to touch) and Investigator's global assessment of response to treatment, the treat-

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ment groups will be compared using the Mantel-Haenszel chi-square test stratified on study site.

Safety assessments will be made based on patient and Investigator inputs. Patients will be initially screened in the clinic for inclusion by review of medical history and concomitant medication use, physical examination, measurement of vital signs (oral temperature, sitting radial or brachial pulse rate, respiratory rate, and sitting blood pressure), body weight, and clinical laboratory testing (serum biochemistry, complete blood count, and urinalysis). After randomization, clinical laboratory tests, concomitant medication use, medical history and current complaints (AE) will be reviewed every 3 months until an acute gout flare occurs in order to ensure continued eligibility. Compliance with key inclusion/exclusion criteria (based on intervening medical history and concomitant medication use) will be reconfirmed by the Gout Flare Call Center prior to authorizing the start of study drug. Following the start of study drug, patients will record any severe gastrointestinal AEs on their diaries and these will be recorded in the Case Report Form (CRF) at each clinic visit. Full physical examinations and clinical laboratory testing will be conducted at the final clinic visit (Visit 4 or Visit 5). Vital signs and body weight will be measured at each Post Flare visit (Visit 3 and 4 or 5). For those patients in whom there is an unresolved AE or clinically significant treatment emergent laboratory abnormality, there will be one additional follow up visit 14 days post flare onset (Visit 6).

Safety analysis will be performed by coding adverse events using a standardized medical dictionary and the incidence summarized by treatment group; tabulations will be prepared of all AEs as well as by relationship and by severity. Adverse events resulting in termination and events meeting regulatory criteria for seriousness will also be tabulated separately. Descriptive statistics (mean, median, standard deviation, and range) of clinical laboratory testing results and vital sign measurements will be generated for each treatment group and change from the most recent value prior to onset of the acute gout flare calculated; no inferential testing will be performed. Treatment emergent abnormalities on physical examination will be tabulated and listed by treatment group. By patient listings of all safety data and concomitant medication use will be generated.

#### Study Results

The following data were obtained in general accordance with the above protocol.

Out of 813 patients screened, 575 were randomized to treatment with 185 patients having a gouty flare and receiving study drug. The intent-to-treat population consisted of 184 patients (52 received standard dose, 74 received low dose and 58 received placebo).

Number of Responders Based on Target Joint Pain Score at 24 Hours Post First Dose					
Colchicine Dose		Placebo	Odds Ratio		
Low (N = 74)	High (N = 52)	(N = 58)	(95% Confidence Intervals)		
N (%)	N (%)	N (%)	Low vs. Placebo	High vs. Placebo	High vs. Low
28 (37.8)	17 (32.7)	9 (15.5)	3.31 (1.41, 7.77)	2.64 (1.06, 6.62)	0.80 (0.38, 1.68)
			P = 0.0046	P = 0.0343	P = 0.5529

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Cumulative Distribution of Degree of Percent Improvement for Target Joint Pain Score at 24 Hours Post First Dose Colchicine Dose				5	Cumulative Distribution of Degree of Percent Improvement for Target Joint Pain Score at 24 Hours Post First Dose Colchicine Dose			
% Improvement	High (N = 52)	Low (N = 74)	Placebo (N = 58)		% Improvement	High (N = 52)	Low (N = 74)	Placebo (N = 58)
>=0%	52 (100.0%)	74 (100.0%)	58 (100.0%)	10	>=60%	15 (28.8%)	24 (32.4%)	7 (12.1%)
>=10%	32 (61.5%)	47 (63.5%)	24 (41.4%)		>=70%	10 (19.2%)	20 (27.0%)	4 (6.9%)
>=20%	29 (55.8%)	45 (60.8%)	21 (36.2%)		>=80%	9 (17.3%)	15 (20.3%)	3 (5.2%)
>=30%	21 (40.4%)	39 (52.7%)	17 (29.3%)		>=90%	6 (11.5%)	9 (12.2%)	2 (3.4%)
>=40%	21 (40.4%)	36 (48.6%)	14 (24.1%)		>=100%	6 (11.5%)	8 (10.8%)	2 (3.4%)
>=50%	19 (36.5%)	30 (40.5%)	10 (17.2%)					

Treatment Response Based on at Least a 2-Unit Reduction in Target Joint Pain Score at 24 Hours and 32 Hours Post First Dose						
Hours Post First Dose	Number (%) of Responders			Treatment Comparisons		
	Colchicine Dose			(Odds Ratio and 95% CI) <sup>1</sup>		
	High (N = 52)	Low (N = 74)	Placebo (N = 58)	High vs. Placebo	Low vs. Placebo	High vs. Low
24	18 (34.6)	32 (43.2)	10 (17.2)	2.54 (1.04, 6.18) p = 0.0368	3.66 (1.61, 8.32) p = 0.0015	0.69 (0.33, 1.45) p = 0.3298
32	20 (38.5)	34 (45.9)	10 (17.2)	3.00 (1.24, 7.24) p = 0.0126	4.08 (1.80, 9.27) p = 0.0005	0.74 (0.36, 1.51) p = 0.4033

<sup>1</sup>The p-value is from the unstratified Pearson chi-square test.

Target Joint Pain at Baseline, 24 Hours and 32 Hours Post First Dose, and Change from Baseline (LOCF) - ITT Population							
Time Point	Statistic	Colchicine Dose			Treatment Comparisons <sup>1</sup>		
		High (N = 52)	Low (N = 74)	Placebo (N = 58)	High vs. Placebo	Low vs. Placebo	High vs. Low
24 Hours Post First Dose							
Baseline	Mean (SD)	6.9 (1.59)	6.9 (1.72)	6.8 (1.44)	-1.3	-1.5	0.2
	Median (Mix, Max)	7.0 (4, 10)	7.0 (4, 10)	7.0 (4, 10)	p = 0.0145	p = 0.0055	p = 0.7540
Change	Mean (SD)	-2.0 (2.93)	-2.2 (3.46)	-0.7 (2.77)			
	Median (Mix, Max)	-2.0 (-9, 4)	-2.0 (-9, 5)	-0.0 (-8, 4)			
32 Hours Post First Dose							
Baseline	Mean (SD)	6.9 (1.59)	6.9 (1.72)	6.8 (1.44)	-1.6	-1.6	0.1
	Median (Mix, Max)	7.0 (4, 10)	7.0 (4, 10)	7.0 (4, 10)	p = 0.0057	p = 0.0038	p = 0.9238
Change	Mean (SD)	-2.3 (3.05)	-2.4 (3.59)	-0.7 (2.95)			
	Median (Mix, Max)	-2.0 (-9, 3)	-2.5 (-9, 5)	0.0 (-8, 4)			

<sup>2</sup>Tabled values are the difference between treatment groups mean change from baseline and p-value from ANCOVA with treatment group as the independent variable and baseline score as the covariate.

Total Pain Relief (TOTPAR) Based on All Target Joint Pain Scores				
Time Point	Statistic	Colchicine Dose		
		High (N = 52)	Low (N = 74)	Placebo (N = 58)
Hour 24	n	51 <sup>1</sup>	74	58
	Mean (SD)	20.9 (48.42)	30.5 (61.44)	9.5 (45.87)
	Median(Mix, Max)	11.5 (-102, 135)	23.0 (-112, 185)	7.3 (-90, 142)

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Total Pain Relief (TOTPAR) Based on All Target Joint Pain Scores				
Colchicine Dose				
Time Point	Statistic	High (N = 52)	Low (N = 74)	Placebo (N = 58)
Hour 32	n	51	74	58
	Mean (SD)	31.9 (63.83)	45.5 (82.05)	12.2 (59.88)
	Median(Mix, Max)	27.5 (-102, 185)	34.1 (-128, 257)	7.3 (-114, 142)

<sup>1</sup>Patient 1026-1005 did not have a diary and the 24-hour call to the Call Center was 27 hours after the initial call. As indicated in the SAP, the Call Center pain score was not eligible for substitution for the missing diary. This patient has been excluded from the TOTPAR summary.

Number (%) of Patients Using Rescue Medication Up to and Including the 24-Hour Post First Dose Assessment					
Colchicine Dose					
High (N = 52)	Low (N = 74)	Placebo (N = 58)	Treatment Comparison (Odds Ratio and 95% CI)		
n (%)	n (%)	n (%)	High vs. Placebo	Low vs. Placebo	High vs. Low
18 (34.6)	23 (31.1)	29 (50.0%)	0.53 (0.25, 1.14) p = 0.1034	0.45 (0.22, 0.92) p = 0.0273	1.17 (0.55, 2.50) p = 0.6768

Change from Baseline in Target Joint Pain Scores at 24 Hours Post First Dose with Interval of Time of Dose Relative to Flare Onset as Covariate (LOCF) - ITT Population							
		Colchicine Dose			Treatment Comparisons <sup>1</sup>		
	Statistic	High (N = 52)	Low (N = 74)	Placebo (N = 58)	High vs. Placebo	Low vs. Placebo	High vs. Low
Early Treatment Start (within 4 hours)							
Baseline	Mean (SD)	6.9 (1.59)	6.9 (1.72)	6.8 (1.44)	-1.3	-1.5	0.2
	Median	7.0 (4, 10)	7.0 (4, 10)	7.0 (4, 10)	p = 0.0145	p = 0.0055	p = 0.7540
	(Mix, Max)						
Change	Mean (SD)	-2.0 (2.93)	-2.2 (3.46)	-0.7 (2.77)			
	Median	-2.0 (-9, 4)	-2.0 (-9, 5)	-0.0 (-8, 4)			
	(Mix, Max)						
Late Treatment Start (after 4 hours)							
Baseline	Mean (SD)	6.9 (1.59)	6.9 (1.72)	6.8 (1.44)	-1.6	-1.6	0.1
	Median	7.0 (4, 10)	7.0 (4, 10)	7.0 (4, 10)	p = 0.0057	p = 0.0038	p = 0.9238
	(Mix, Max)						
Change	Mean (SD)	-2.3 (3.05)	-2.4 (3.59)	-0.7 (2.95)			
	Median	-2.0 (-9, 3)	-2.5 (-9, 5)	0.0 (-8, 4)			
	(Mix, Max)						

<sup>1</sup>Patient 1016-1013 was missing a flare onset time and Patients 1002-1007, 1018-1008, 1006-1013, 1009-1011, 1010-1005, 1010-1010, 1026-1002, 1026-1007, 1064-1007, and 1068-1022 appear to have taken the first dose of study medication prior to flare onset.

<sup>2</sup>Tabled values are the difference between treatment groups mean change from baseline and p-value from ANCOVA with treatment group as the independent variable and baseline score as the covariate.

Overall Summary of Treatment Emergent Adverse Events - Safety Population			
Colchicine Dose			
	High (N = 52) n (%)	Low (N = 74) n (%)	Placebo (N = 59) n (%)
Total Number of TEAEs <sup>1</sup>	85	34	27
Number (%) of Patients with at Least One TEAE	40 (76.9)	27 (36.5)	16 (27.1)
Number (%) of Patients with at Least One Mild TEAE	15 (28.8)	19 (25.7)	9 (15.3)
Number (%) of Patients with at Least One Moderate TEAE	15 (28.8)	8 (10.8)	6 (10.2)
Number (%) of Patients with at Least One Severe TEAE	10 (19.2)	0	1 (1.7)

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Overall Summary of Treatment Emergent Adverse Events - Safety Population			
	Colchicine Dose		
	High	Low	Placebo
	(N = 52)	(N = 74)	(N = 59)
	n (%)	n (%)	n (%)
Number (%) of Patients with a TEAE Discontinuing Study	0	0	0
Number (%) of Patients with a Treatment Emergent SAE	0	0	0

<sup>1</sup>Patients reporting more than one adverse event are only counted once for a given event.

Number (%) of Patients with at Least One Treatment-Emergent Gastrointestinal Adverse Event Recorded on the Diary or the CRF- Safety Population						
Method of Capture	Colchicine Dose					
	Standard		Low		Placebo	
	(N = 52)		(N = 74)		(N = 59)	
	All	Severe	All	Severe	All	Severe
Captured on Adverse Event CRF <sup>1</sup>	40 (76.9) <sup>2</sup>	10 (19.2)	19 (25.7)	0	12 (20.3)	0
Captured on Patient Diary	48 (92.3) <sup>2</sup>	13 (25.0)	32 (43.2) <sup>3</sup>	3 (4.1)	15 (25.4)	2 (3.4)
Captured on Patient Diary or Adverse Event CRF	49 (94.2) <sup>2</sup>	18 (34.6)	33 (44.6)	3 (4.1)	16 (27.1)	2 (3.4)

<sup>1</sup>Gastrointestinal adverse events captured on the AE CRF include the MedDRA preferred terms of "diarrhoea", "nausea", "vomiting", "abdominal pain", or "abdominal pain lower", "abdominal pain upper", "abdominal discomfort", or "dyspepsia".

<sup>2</sup>Statistically significantly different from placebo and from Low-dose colchicine (95% CI of odds ratio does not include "1").

<sup>3</sup>Statistically significantly different from placebo (95% CI of odds ratio does not include "1").

Number (%) of Patients with at Least One Severe TEAE in Any Treatment Group- Safety Population							
MedDRA System Organ Class MedDRA Preferred Term	Colchicine Dose				Odds Ratio		
	Low		All	Placebo	(95% Confidence)		
	High (N = 52) n (%)	(N = 74) n (%)	Colchicine (N = 126) n (%)	(N = 59) n (%)	High vs. Placebo	Low vs. Placebo	High vs. Low
Number of Patients with at Least One Severe TEAE	10 (19.2)	0	10 (7.9)	1 (1.7)	13.8 (1.7, 112)	—	—
Gastrointestinal Disorders	10 (19.2)	0	10 (7.9)	0	—	—	—
Diarrhea	10 (19.2)	0	10 (7.9)	0	—	—	—
Melaena	1 (1.9)	0	1 (0.8)	0	—	—	—
Nausea	1 (1.9)	0	1 (0.8)	0	—	—	—
Metabolism and Nutrition Disorders	0	0	0	1 (1.7)	—	—	—
Gout	0	0	0	1 (1.7)	—	—	—
Musculoskeletal and Connective Tissue Disorders	1 (1.9)	0	1 (0.8)	0	—	—	—
Pain in Extremity	1 (1.9)	0	1 (0.8)	0	—	—	—

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Number (%) of Patients with at Least One Drug-Related Treatment Emergent Adverse Events with an Incidence of $\geq 2\%$ of Patients in Any Treatment Group						
MedDRA System Organ Class MedDRA Preferred Term	Colchicine Dose		Placebo (N = 59) n (%)	Odds Ratio (95% Confidence Intervals)		
	High (N = 52) n (%)	Low (N = 74) n (%)		High vs. Placebo	Low vs. Placebo	High vs. Low
Number of Patients with at Least One Drug-Related TEAE	38 (73.1)	21 (28.4)	14 (23.7)	8.7 (3.7, 20.6)	1.3 (0.6, 2.8)	6.9 (3.1, 15.2)
Gastro-intestinal Disorders	38 (73.1)	18 (24.3)	11 (18.6)	11.8 (4.8, 29.0)	1.4 (0.6, 3.3)	8.4 (3.8, 19.0)
Diarrhea	38 (73.1)	16 (21.6)	8 (13.6)	17.3 (6.6, 45.4)	1.8 (0.7, 4.4)	9.8 (4.3, 22.5)
Nausea	7 (13.5)	3 (4.1)	3 (5.1)	2.9 (0.7, 11.9)	0.8 (0.2, 4.1)	3.7 (0.9, 15.0)
Vomiting	8 (15.4)	0	0	—	—	—

As shown in the above tables, standard dose colchicine produced  $\geq 50\%$  pain reduction at 24 hrs without pain rescue in a greater proportion of patients than did placebo (32.7% vs. 15.5%,  $p=0.0343$ ; odds ratio 2.64 (95% CI, 1.06, 6.62), and more gastrointestinal side effects than placebo (73.1% vs. 18.6%, odds ratio 11.8 {95% CI, 4.8, 29.0}), in particular more diarrhea than placebo (73.1% vs. 13.6%, odds ratio 17.3 {95% CI, 6.6, 45.4}). Low dose colchicine also produced  $\geq 50\%$  pain reduction at 24 hrs without pain rescue in a greater proportion of patients than did placebo (37.8% vs. 15.5%,  $p=0.0046$ ; odds ratio 3.31 (95% CI, 1.41, 7.77)), and more gastrointestinal side effects than placebo (24.3% vs. 18.6%, odds ratio 1.4 {95% CI, 0.7 to 11.9}), but did not significantly differ from placebo with respect to diarrhea (21.6% vs. 13.6%, odds ratio 1.8 {95% CI, 0.7 to 4.4}). Severe diarrhea occurred in 19.2% of patients taking high-dose colchicine while not occurring in the low-dose colchicine group. Vomiting occurred in 15.4% of patients taking high-dose colchicine while not occurring in the low-dose colchicine group.

Based on the primary efficacy variable of  $\geq 50\%$  pain reduction at 24 hrs without pain rescue, the proportion of responders to the standard dose and the low dose colchicine regimens was not significantly different ( $p=0.5529$ ). The odds ratio for being a responder to standard dose colchicine vs. being a responder to low dose colchicine was 0.80 (95% CI, 0.38, 1.68). The proportion of patients rescued prior to 24 hours for the standard dose, low dose and placebo were 34.6%, 28.4% and 48.3%, respectively.

FIG. 1 summarizes efficacy data from the trial. FIG. 1 shows the fraction of all patients improved at 24 hrs post-first dose, regardless of pain rescue, as a function of the percent improvement in pain for each of the three treatment methods (standard dose, low dose, placebo). For example, 49% of patients taking the low dose achieved at least 40% relief compared to 24% of the patients on placebo.

Standard dose oral colchicine was established to be effective, but burdened by significant diarrhea. In contrast, although low dose colchicine was not significantly different from standard dose colchicine in efficacy, low dose colchicine was not significantly different from placebo with respect to diarrhea. This trial provides a new evidence basis for acute gout treatment, specifically supporting the unexpected superiority of a low dose colchicine dosing regimen of 2 tablets of

0.6 mg followed in 1 hour by 1 tablet. The higher standard dose colchicine dosing regimen did not improve patient outcome, but did increase adverse events.

#### Example 4

##### Pharmacokinetic Study in Healthy Adults of Single vs. Multiple Oral Doses of Colchicine Tablets

This study was a single-center, open-label, single-sequence, two-period study to evaluate the pharmacokinetic profile of colchicine following single and multiple oral doses of colchicine tablets, 0.6 mg, in healthy volunteers.

In Period 1, study subjects received a 0.6-mg dose of colchicine after an overnight fast of at least 10 hours. In Period 2, subjects received a 0.6-mg dose of colchicine in the morning and the evening (approximately 12 hours later) for 10 days (steady state regimen). Subjects received a light breakfast served 60 minutes following dose administration in the morning and the evening dose was administered 90 minutes after an evening meal on Days 15 through 24 only. On Day 25, the colchicine dose was administered after an overnight fast of at least 10 hours and lunch was served 4 hours post-dose. Study periods were separated by a 14-day wash-out. Following the single dose and the last dose of the multiple dose regimen (beginning on the mornings of Day 1 and Day 25, respectively), blood samples were collected (6 mL each) from each subject within 1 hour prior to dosing and after dose administration at study hours 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 (while confined) and 36, 48, 72, and 96 (on an outpatient basis). Plasma concentrations of colchicine and its metabolites were determined using validated LC/MS-MS methods.

Thirteen healthy, non-smoking subjects with a mean age of 25.5 years (range 19 to 38 years) and within 15% of ideal body weight were enrolled in this study. All subjects completed both dosing periods according to protocol.

After a single dose, plasma concentrations are no longer quantifiable 24 hours post-dose in all but 1 subject. After the last dose of the steady state regimen, concentrations remained quantifiable for 48 to 72 hours. Review of individual subject data shows that no subject experienced a secondary colchicine peak, either following a single dose or upon multiple dosing.

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All 2-O-demethylcolchicine (2-DMC) concentrations were below the level of quantitation (LOQ, 0.2 ng/mL) and only one sample from 1 subject (of 13 subjects) had a detectable 3-O-demethylcolchicine (3-DMC) concentration which was near the level of quantitation. Therefore, metabolites are not discussed further.

In healthy adults, colchicine appears to be readily absorbed when given orally, reaching a mean maximum plasma concentration of 2.5 ng/mL in 1.5 hours after a single dose. The drug is distributed widely, with an apparent volume of distribution of 540 L, greatly exceeding total body water. The elimination half-life as calculated following a single oral dose is approximately 5 hours. Levels were not detectable by 24 hours post-dose and this is therefore not an accurate estimate. Pharmacokinetic parameter values are summarized in the table below.

Review of trough plasma concentrations indicates that steady state was attained by approximately the eighth day of dosing for most subjects. Colchicine may have a diurnal variation reflected in the observed C<sub>min</sub> concentrations at steady state. C<sub>min</sub> concentrations prior to the morning dose are approximately 12% higher than the C<sub>min</sub> concentrations prior to the evening dose (Day 23 and Day 24). The mean C<sub>min</sub> concentration observed on Day 25 was 0.907 ng/mL.

Colchicine accumulated following administration of multiple doses to an extent greater than expected. Exposure was nearly two-fold higher (approximately 1.7 based on AUC [Day 25 AUC<sub>0-τ</sub>/Day 1 AUC<sub>0-∞</sub>] and approximately 1.5 based on C<sub>max</sub> [Day 25 C<sub>max</sub>/Day 1 C<sub>max</sub>]). This observation could be attributable to an underestimation of AUC<sub>∞</sub> following a single dose. With the higher plasma levels that occur with repeated dosing, a longer terminal elimination half life is apparent, 26.6 hours. Pharmacokinetic parameter values are summarized in the tables below.

TABLE 10

Colchicine Pharmacokinetic Parameter Values Following Administration of A Single Oral Dose of Colchicine 0.6 mg in Healthy Adults						
	AUC <sub>0-t</sub> (pg-hr/mL)	AUC <sub>0-inf</sub> (pg-hr/mL)	C <sub>max</sub> (pg/mL)	T <sub>max</sub> (hr)	Kel (1/hr)	T <sub>1/2</sub> (hr)
N	13	13	13	13	13	13
MEAN	10508.54	12281.90	2470.77	1.50	0.1829	4.95
STDEV	3544.82	4423.34	706.98	0.54	0.0592	4.43
% CV	33.73	36.02	28.61	36.00	32.39	89.54
MEDIAN	10560.90	11451.45	2714.00	1.50	0.1992	3.48
MIN	4812.88	7252.66	1584.00	1.00	0.0359	2.84
MAX	18128.65	23838.48	3977.00	3.00	0.2443	19.29

TABLE 11

Colchicine Pharmacokinetic Parameter Values Following Administration of Multiple (b.i.d.) Oral Doses of Colchicine 0.6 mg in Healthy Adults									
	AUC <sub>0-t</sub> (pg-hr/mL)	AUC <sub>0-τ</sub> (pg-hr/mL)	AUC <sub>0-inf</sub> (pg-hr/mL)	C <sub>max</sub> (pg/mL)	C <sub>min</sub> (pg/mL)	C <sub>ave</sub> (pg/mL)	T <sub>max</sub> (hr)	Kel (1/hr)	T <sub>1/2</sub> (hr)
N	13	13	13	13	13	13	13	13	13
MEAN	43576.96	29056.23	54198.77	3553.15	906.51	1210.68	1.31	0.03	26.60
STDEV	9333.26	4531.30	9214.54	843.45	152.19	188.80	0.60	0.00	4.33
% CV	21.42	15.59	17.00	23.74	16.79	15.59	45.61	16.34	16.26
MEDIAN	41925.10	28452.15	54113.43	3734.00	903.50	1185.51	1.00	0.03	26.51
MIN	29328.78	20791.98	37599.76	1977.00	636.23	866.33	0.50	0.02	20.82
MAX	58265.35	36083.95	67944.65	4957.00	1149.67	1503.50	3.00	0.03	33.65

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TABLE 12

Mean (% CV) Colchicine Pharmacokinetic Parameter Values Following Administration of Single and Multiple (b.i.d.) Oral Doses of Colchicine 0.6 mg in Healthy Adults		
	V <sub>d</sub> /F(L)	CL/F (L/hr)
Colchicine 0.6-mg Single Dose (N = 13)		
Day 1	341 (54.4)	54.1 (31.0)
Colchicine 0.6 mg b.i.d. x 10 days		
Day 25	1150 (18.73)	30.3 (19.0)

CL = Dose/AUC<sub>0-τ</sub> (Calculated from mean values)

V<sub>d</sub> = CL/K<sub>e</sub> (Calculated from mean values)

In the above table, the parameter CL/F denotes the apparent total body clearance after administration, calculated as Total Dose/Total AUC<sub>0-τ</sub>; and V<sub>d</sub>/F denotes the apparent total volume of distribution after administration, calculated as Total Dose/(Total AUC<sub>∞</sub> × K<sub>e</sub>).

## Example 5

## Pharmacokinetic Study in Healthy Adults of Low Dose Acute Gout Regimen: 1.8 mg Over 2 Hours

This study was a single-center, single-period, open-label pharmacokinetic study conducted in healthy subjects under fasting conditions. It was designed to characterize the pharmacokinetic profile of a low-dose regimen of colchicine (1.8 mg over 2 hours) used as one of the treatment arms in the randomized, controlled trial in patients with an acute gout flare discussed above.

Thirteen healthy, non-smoking subjects with a mean age of 29.3 years (range 20 to 49 years) and within 15% of ideal body weight were enrolled in this study. Subjects received 2x0.6 mg tablets initially followed by 1x0.6 mg tablet 1 hour later. Blood samples for measurement of colchicine plasma concentrations and metabolites were collected (relative to the first dose of study drug) at pre-dose; 0.5 and 1 hour post-dose (prior to second dose); and 1.5, 2, 2.5, 3, 4, 6, 8, 12, 18, 24, 36, and 48 hours post-dose. Subjects were confined until 48 hours post-dose and then returned 72 and 96 hours after the first dose for additional blood sampling on an outpatient basis. Plasma concentrations of colchicine and its metabolites were determined using validated LC/MS-MS methods.

2-DMC concentrations were below the LOQ for all subjects. Eight of 13 subjects had at least one measurable 3-DMC concentration (29 total 3-DMC measurable concentrations). 3-DMC concentrations ranged from 0.20 ng/mL (near the LOQ) to 0.45 ng/mL and were observed 1 to 4 hours post-dose. Given these low levels, metabolites are not discussed further herein.

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When colchicine was administered in this low-dose regimen, concentrations increased to a maximum of 6.2 ng/mL, occurring 1.81 hours after the initial dose (0.81 hours after the second dose). Most of the subjects (10 of 13 subjects or 77%) experienced a secondary peak within 6 hours after the first of the two doses, attributed to intestinal secretion and re-absorption and/or biliary recirculation.

The terminal elimination half-life was 23.6 hours. A summary of the pharmacokinetic parameter values is provided in the table below.

TABLE 12

	$C_{max}$ (pg/mL)	$T_{max}$ (hr)	Total AUC <sub>0-t</sub> (pg-hr/mL)	Total AUC <sub>∞</sub> (pg-hr/mL)	$K_{el}$ (1/hr)	CL/F (mL/hr)	$V_{area}/F$ (L)	$t_{1/2}$ (hr)
N	13	13	13	13	13	13	13	13
MEAN	6192.77	1.81	43787.55	52070.06	0.0326	36950.93	1188.72	23.63
STDEV	2433.70	0.38	11437.48	13689.27	0.0100	9993.17	319.56	9.24
% CV	39.30	21.24	26.12	26.29	30.80	27.04	26.88	39.10
MEDIAN	5684.00	2.00	43942.15	50783.77	0.0322	35444.40	1149.35	21.56
MIN	3160.00	1.00	28821.45	34171.00	0.0141	24295.73	774.19	13.80
MAX	11370.00	2.50	58931.99	74087.08	0.0502	52676.24	1724.36	49.20

## Example 6

Pharmacokinetic Study in Healthy Adults of a  
Standard-Dose Acute Gout Regimen: 4.8 mg  
Colchicine over 6 Hours

This study was a single center, randomized, double-blind, double-dummy pharmacokinetic and exploratory ECG safety study.

With respect to the pharmacokinetic aspect of the study, on Day 1, following a minimum of 10 hours overnight fast, subjects received the appropriate randomized study drug (combination of over-encapsulated active drug or placebo capsules such that the blind was preserved). Those randomized to colchicine received 4.8 mg over 6 hours (initially

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8, 10, 12, 23, 36, 48, 72 and 96 hours post-dose. Subjects were confined until 48 hours post-dose and then returned 72 and 96 hours after the first dose for additional blood sampling on an outpatient basis. Plasma concentrations of colchicine and its metabolites were determined using validated LC/MS-MS methods.

Eighteen healthy, non-smoking subjects with a mean age of 28.7 years (range 18 to 50 years) and within 15% of ideal body weight were enrolled in this study. Fifteen subjects were

randomized to receive colchicine and 3 subjects were randomized to receive moxifloxacin as a positive control for QTc prolongation. All subjects completed the study according to protocol.

When colchicine was administered as the standard-dose regimen used in the treatment of patients experiencing an acute gout flare, colchicine concentrations increased to a maximum of 6.8 ng/mL (similar to the reported C<sub>max</sub> in the low-dose regimen) and absorbed approximately 4.5 hours after the initial dose (3.5 hours after the second dose). Most of the subjects (13 of 15 subjects receiving colchicine or 87%) experienced a secondary peak within 6 hours after a single oral dose, attributed to intestinal secretion and re-absorption and/or biliary recirculation. The terminal elimination half-life was 31.38 hours. A summary of the pharmacokinetic parameter values is provided in the table below.

TABLE 13

	$C_{max}$ (ng/mL)	$T_{max}$ (hr)	Total AUC <sub>0-t</sub> (ng-hr/mL)	Total AUC <sub>∞</sub> (ng-hr/mL)	$K_{el}$ (h <sup>-1</sup> )	CL/F (mL/hr)	$V_{area}/F$ (L)	$t_{1/2}$ (hr)
N	15	15	15	15	15	15	15	15
MEAN	6.84	4.47	104.95	118.20	0.0242	43168.87	1876.09	31.38
STDEV	1.30	1.99	24.61	26.01	0.0088	12862.03	456.19	8.36
% CV	18.94	44.65	23.45	22.01	36.59	29.79	24.32	26.65
MEDIAN	6.69	3.12	113.12	126.47	0.0212	37954.71	1902.14	32.76
MIN	4.95	3.12	53.74	61.31	0.0147	31386.01	805.92	15.03
MAX	8.60	7.50	138.24	152.93	0.0461	78287.41	2639.21	47.22

2×0.6 mg tablets followed by 1×0.6 mg tablet every hour for six additional doses). Those randomized to moxifloxacin received 1×400 mg tablet. Both dosing regimens were followed by a 4-hour post-dose fast (post-dose fast for colchicine arm started after the first dose of colchicine administered). Blood samples were obtained on Day 1 at the following time points (relative to the first dose of study drug): pre-dose and 1 (prior to second dose), 3 (prior to fourth dose), 6 (prior to final dose), 6.17, 6.33, 6.5, 6.75, 7, 7.25, 7.5, 7.75,

2-DMC concentrations were below LOQ for all subjects. Fourteen of 15 subjects had at least one measurable 3-DMC concentration; the 3-DMC concentrations ranged from 0.25 ng/mL (near the LOQ) to 0.42 ng/mL and were observed 1.12 to 12.12 hours post-dose. Summary mean 3-DMC pharmacokinetic parameter values can be found in the table below. The observed mean 3-DMC C<sub>max</sub>, AUC<sub>0-t</sub>, and AUC<sub>∞</sub> concentrations were approximately 4.7%, 2%, and 4.1% of the observed mean colchicine C<sub>max</sub>, AUC<sub>0-t</sub>, AUC<sub>∞</sub> concentrations, respectively.

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TABLE 14

Mean (% CV) 3-DMC Pharmacokinetic Parameter Values after Standard-Dose Colchicine (4.8 mg over 6 hours) Administration in Healthy Adults					
	$C_{max}$ (ng/mL)	$T_{max}$ <sup>1</sup> (h)	$AUC_{0-t}$ (ng · h/mL)	$AUC_{\infty}$ (ng · h/mL)	$Ke$ (h <sup>-1</sup> )
	N = 15	N = 14	N = 13	N = 8	N = 8
Standard Dose N = 15	0.32 (16.35)	5.06 (3.12-8.12)	2.09 (40.29)	4.84 (42.73)	0.1418 (60.15)
					6.93 (64.35)

<sup>1</sup> $T_{max}$  reported mean (range)

## Example 7

Food Effect Study Single Dose vs.  
COL-PROBENECID® (0.5 mg Colchicine/500 mg  
Probenecid)

The clinical study of this example was a randomized, single-dose, three-way crossover study testing the bioequivalence of two formulations of colchicine administered under standard fasting conditions, one the 0.6 mgA colchicine formulation of Example 2 (test product) and one a marketed combination product, 0.5 mg colchicine/500 mg probenecid tablets (COL-PROBENECID®, Watson Laboratories, Inc.) (reference product), and the effect of food on the test product by dosing following a high-fat breakfast.

Twenty-eight healthy non-smoking adult volunteers (male and female) and no alternates initiated the study. Subjects received three single doses, in a randomized sequence of three treatment periods. On each occasion, subjects received either one colchicine tablet USP, 0.6 mg (test product) given either with food or in a standard fasting condition or one colchicine 0.5 mg/probenecid 500 mg tablet (reference product) given in a standard fasting condition. Each treatment period was separated by a 14-day washout.

The two dosing conditions were (1) Standard Fasting Conditions (either colchicine tablets USP, 0.6 mg (test A) or reference product, COL-PROBENECID®): 1 tablet of test product (Test A) or reference product with 240 mL of room temperature water after an overnight fast of at least 10 hours; subjects will continue to fast for 4 hours post-dose; and (2) High-fat Breakfast (colchicine tablets USP, 0.6 mg): 1 tablet of test product (Test B) with 240 mL of room temperature water 30 minutes after initiation of a standardized, high-fat and high-calorie breakfast (FDA standard meal) preceded by an overnight fast.

Subjects were confined for at least 15 hours prior to and until at least 24 hours after dosing each period. During each period, subjects returned on four separate occasions for outpatient blood sampling.

No fluid, except that given with drug administration and the standardized high-fat and high-calorie breakfast (FDA standard meal) depending on the randomization, was allowed from 1 hour prior to dose administration until 2 hours after dosing. When fluids were restricted, they will be allowed ad libitum but will generally be controlled.

Dinner was served approximately 13.5 hours prior to dose administration. At 30 minutes before dose administration, those subjects to be dosed after eating (depending on randomization) were served the standardized, high-fat and high-calorie breakfast (FDA standard meal). All subjects fasted for at least 4 hours after dosing. Clear fluids, such as water, were allowed during fasting.

Subjects were served standardized meals and beverages, controlled by the clinic during periods of confinement. Meals were the same in content and quantity during each confinement period. No grapefruit and/or grapefruit containing products or caffeine and/or xanthine containing products were allowed during the confinement portions of the study.

During confinement, only non-strenuous activity was permitted. Following dose administration, subjects remained in a seated or upright position for at least 4 hours to ensure proper gastric emptying and subject safety.

Blood (6 mL) was collected in K2 EDTA vacutainers with samples taken within 1 hour prior to dosing (0 hour) and after dose administration at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours (while confined) and 36, 48, 72, and 96 hours (on an outpatient basis). 1. Colchicine and metabolite plasma concentrations (colchicine, 2-DMC, 3-DMC, and 10 demethylcolchicine) were measured using a validated bioanalytical method.

Pharmacokinetic results comparing the test product under fed and fasting conditions are shown below.

TABLE 15

Pharmacokinetic results of colchicine test product under fed and fasting						
Ln-Transformed Data						
PK Variable	Least Squares Mean		Geometric Mean		90% Confidence Interval (Lower Limit, Upper Limit)	
	Test B	Test A	Test B	Test A	% Ratio	
$C_{max}$ (ng/mL)	7.784	7.781	2402.55	2393.60	100.37	(89.84, 112.14)
$AUC_{0-t}$ (ng/mL-hr)	9.201	9.334	9906.40	11310.90	87.58	(78.07, 98.26)
$AUC_{0-inf}$ (ng/mL-hr)	9.300	9.468	10939.73	12939.64	84.54	(76.73, 93.15)

Geometric means are based on least squares means of In-transformed values.

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TABLE 15-continued

Non-Transformed Data				
PK Variable	Least Squares Mean		90% Confidence Interval	
	Test B	Test A	% Ratio	(Lower Limit, Upper Limit)
$C_{max}$ (pg/mL)	2486.99	2493.15	99.75	(90.43, 109.07)
$AUC_{0-t}$ (pg/mL-hr)	10438.89	12536.56	83.27	(72.79, 93.74)
$AUC_{0-inf}$ (pg/mL-hr)	11345.62	13907.83	81.58	(71.53, 91.63)
$T_{max}$ (hr)	1.85	1.35	137.14	(111.11, 163.17)
Kel (hr <sup>-1</sup> )	0.1902	0.1520	125.13	(107.67, 142.58)
$T_{1/2}$ (hr)	4.34	6.27	69.17	(45.2, 93.14)

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TABLE 16

Descriptive statistics for Pharmacokinetic Parameters for Test Product A (0.6 mg) - Fasting conditions			
	$AUC_{0-t}$ (pg-hr/mL)	$AUC_{0-inf}$ (pg-hr/mL)	$C_{max}$ (pg/mL)
N	25	24	25
Arithmetic Mean	12589	14113	2503
STDev	6210.729	5595.398	722.049
% CV	48.621	39.648	28.847
Median	11412.80	12756.02	2473.00
Min	4430.73	6674.96	1291.00
Max	30787.30	27789.51	3989.00

TABLE 17

Descriptive statistics for Pharmacokinetic Parameters for Test Product A (0.6 mg) - Fed conditions			
	$AUC_{0-t}$ (pg-hr/mL)	$AUC_{0-inf}$ (pg-hr/mL)	$C_{max}$ (pg/mL)
N	25	22	25
Arithmetic Mean	10491	11404	2497
STDev	4024.804	2895.681	695.091

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TABLE 17-continued

Descriptive statistics for Pharmacokinetic Parameters for Test Product A (0.6 mg) - Fed conditions			
	$AUC_{0-t}$ (pg-hr/mL)	$AUC_{0-inf}$ (pg-hr/mL)	$C_{max}$ (pg/mL)
% CV	38.374	25.392	27.838
Median	9556.25	10964.17	2293.00
Min	6168.53	7128.50	1256.00
Max	26031.15	20101.33	3930.00

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Food was observed to have negligible effect on rate of absorption, as indicated by the percent ratio of ln-transformed  $C_{max}$  data of 100.37, but decreased the extent of absorption by about 15%, as indicated by the percent ratio of ln-transformed  $AUC_{0-t}$  and  $AUC_{0-inf}$  values of 87.56 and 84.54, respectively. Under fasted and fed conditions, the mean  $C_{max}$  was 2.5 ng/mL.  $T_{max}$  was 1.35 hrs under fasted conditions and 1.85 hrs under fed conditions.

Pharmacokinetic results comparing the test product to the reference product are shown in the tables below. The difference in colchicine potency of the test and reference products was corrected by calculating dose-normalized values in the pharmacokinetic parameters.

TABLE 18

Summary of Statistical Analysis Colchicine Test Product A (0.6 mg) - Fasting vs Reference Product C (0.5 mg) - Fasting (Dose Normalized to 0.5 mg) N = 25						
Ln-Transformed Data						
PK Variable	Least Squares Mean		Geometric Mean		% Ratio	90% Confidence Interval (Lower Limit, Upper Limit)
	Test A	Reference C	Test A	Reference C		
$C_{max}$ (pg/mL)	7.598	7.374	1994.67	1594.51	125.10	(111.97, 139.76)
$AUC_{0-t}$ (pg/mL-hr)	9.151	8.833	9425.75	6858.61	137.43	(122.5, 154.18)
$AUC_{0-inf}$ (pg/mL-hr)	9.286	8.970	10783.03	7863.34	137.13	(124.46, 151.09)
Geometric means are based on least squares means of ln-transformed values.						
Non-Transformed Data						
PK Variable	Least Squares Mean		90% Confidence Interval		% Ratio	(Lower Limit, Upper Limit)
	Test A	Reference C	Test A	Reference C		
$C_{max}$ (pg/mL)	2076.08	1688.54	122.95			(110.07, 135.83)
$AUC_{0-t}$ (pg/mL-hr)	10435.91	8016.44	130.18			(115.25, 145.11)
$AUC_{0-inf}$ (pg/mL-hr)	11565.28	8230.68	140.51			(126.04, 154.99)
$T_{max}$ (hr)	1.35	1.34	100.11			(74.05, 126.17)
Kel (hr <sup>-1</sup> )	0.1520	0.1970	77.16			(63.69, 90.63)
$T_{1/2}$ (hr)	6.27	3.78	165.89			(126.13, 205.65)

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The 0.6 mgA colchicine tablet, formulated as in Example 2, showed enhanced bioavailability over COL-PROBENECID®. The formulation disclosed herein showed a greater rate and extent of absorption than did the COL-PROBENECID®.

Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. The endpoints of all ranges directed to the same component or property are inclusive and independently combinable.

All methods described herein can be performed in a suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") provided herein, is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the invention as used herein. Unless defined otherwise, technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs. The terms wt %, weight percent, percent by weight, etc. are equivalent and interchangeable.

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Embodiments of this invention are described herein, including the best mode known to the inventors for carrying out the invention. Variations of those preferred embodiments may become apparent to those of ordinary skill in the art upon reading the foregoing description. The inventors expect skilled artisans to employ such variations as appropriate, and the inventors intend for the invention to be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.

I claim:

1. A method of treating a gout flare with colchicine in a patient undergoing colchicine prophylactic treatment of gout flares, consisting of

administering to a patient having a gout flare while undergoing prophylactic treatment of gout flares

1.2 mgA oral colchicine at the onset of the acute gout flare, followed by 0.6 mgA oral colchicine about one hour later; and

after waiting 12 hrs, continuing prophylactic treatment consisting of 0.6 mgA or 1.2 mgA oral colchicine daily.

\* \* \* \* \*

UNITED STATES PATENT AND TRADEMARK OFFICE  
**CERTIFICATE OF CORRECTION**

PATENT NO. : 7,981,938 B2  
APPLICATION NO. : 12/687406  
DATED : July 19, 2011  
INVENTOR(S) : Matthew W. Davis

Page 1 of 2

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In column 1, line 25, delete "N-[7S," and insert -- N-[(7S, --, therefor.

In column 5, line 48, delete "mitotis," and insert -- mitosis, --, therefor.

In column 10, line 9, delete "HPLC" and insert -- UPLC --, therefor.

In column 10, line 65, "(HPLC)" and insert -- (UPLC) --, therefor.

In column 14, line 8, delete "manufacture" and insert -- manufacture. --, therefor.

In column 14, line 30, delete "N-formyldeactylcholchicine," and insert  
-- N-formyldeacetylcolchicine, --, therefor.

In column 16, line 20, delete "composition" and insert -- composition. --, therefor.

In column 16, line 26, delete "alignates," and insert -- alginates --, therefor.

In column 16, line 46-47, delete "crosscarmellose" and insert -- croscarmellose --, therefor.

In column 18, line 36, delete "HPLC" and insert -- UPLC --, therefor.

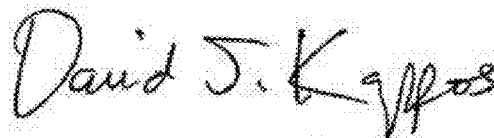
In column 20, line 62, delete "0.5%" and insert -- 0.5%. --, therefor.

In column 22, line 22, delete "Buffer:methanl" and insert -- Buffer:methanol --, therefor.

In column 22, line 58, delete "Volumentric" and insert -- Volumetric --, therefor.

In column 22, line 62, delete "Volumentric" and insert -- Volumetric --, therefor.

Signed and Sealed this  
Twenty-second Day of November, 2011

A handwritten signature in black ink that reads "David J. Kappos". The signature is written in a cursive, flowing style.

David J. Kappos  
*Director of the United States Patent and Trademark Office*

**CERTIFICATE OF CORRECTION (continued)**

Page 2 of 2

**U.S. Pat. No. 7,981,938 B2**

In column 27, line 61, delete “1βscreen” and insert -- 1A screen --, therefor.

In column 28, line 67, delete “probenicid.” and insert -- probenecid. --, therefor.

In column 35, line 17, before “hours” insert -- 12 --.

In column 37-38, line 39, delete “goup” and insert -- group --, therefor.

In column 45, line 4, delete “3-O-demethylcolchcine” and insert -- 3-O-demethylcolchicine --, therefor.

UNITED STATES PATENT AND TRADEMARK OFFICE  
**CERTIFICATE OF CORRECTION**

PATENT NO. : 7,981,938 B2  
APPLICATION NO. : 12/687406  
DATED : July 19, 2011  
INVENTOR(S) : Matthew W. Davis

Page 1 of 3

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In column 3, line 20, delete "Cmax" and insert --  $C_{\max}$  --, therefor.

In column 4, line 24, delete "Cmax" and insert --  $C_{\max}$  --, therefor.

In column 4, line 39, delete "Cmax" and insert --  $C_{\max}$  --, therefor.

In column 4, line 49, delete "Cmax" and insert --  $C_{\max}$  --, therefor.

In column 4, line 50, delete "Cmax" and insert --  $C_{\max}$  --, therefor.

In column 13, line 49, delete "4000 mL" and insert -- 400 mL --, therefor.

In column 18, line 18, delete "Impurity B." and insert -- Impurity B, --, therefor.

In column 22, line 6, after "USP/30NF25" insert -- . --.

In column 29, line 8, delete "(Probenecid" and insert -- (Probenicid --, therefor.

In column 31, line 29, delete "levels to undetectable" and insert -- undetectable --, therefor.

In column 34, line 10, delete "also be," and insert -- also --, therefor.

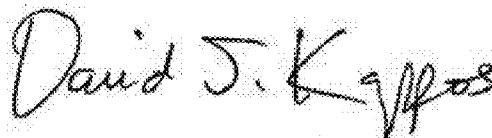
In column 37, line 54, delete "<sup>2</sup>Tabled" and insert -- <sup>1</sup>Tabled --, therefor.

In column 39, line 51, delete "<sup>1</sup>Patient" and insert -- Patient --, therefor.

In column 39, line 53, delete "<sup>2</sup>Tabled" and insert -- <sup>1</sup>Tabled --, therefor.

In column 45, line 22, delete "Cmin" and insert --  $C_{\min}$  --, therefor.

Signed and Sealed this  
Third Day of July, 2012

A handwritten signature in black ink, reading "David J. Kappos". The signature is written in a cursive, flowing style with a large initial "D".

David J. Kappos  
*Director of the United States Patent and Trademark Office*

**CERTIFICATE OF CORRECTION (continued)**

Page 2 of 3

**U.S. Pat. No. 7,981,938 B2**

In column 45, line 23, delete “Cmin” and insert --  $C_{\min}$  --, therefor.

In column 45, line 24, delete “Cmin” and insert --  $C_{\min}$  --, therefor.

In column 45, line 26, delete “Cmin” and insert --  $C_{\min}$  --, therefor.

In column 45, line 33, delete “AUC $\infty$ ” and insert --  $AUC_{\infty}$  --, therefor.

In column 45, line 43, delete “Kel” and insert --  $K_{el}$  --, therefor.

In column 46, line 1, after “Table 12” insert -- A --.

In column 46, line 6, delete “Vd” and insert --  $V_d$  --, therefor.

In column 46, line 14, delete “Vd = CL/K<sub>e</sub>” and insert --  $V_d = CL/K_e$  --, therefor.

In column 46, line 17, delete “AUC<sub>0-tau</sub>” and insert --  $AUC_{0-\tau}$  --, therefor.

In column 46, line 59, delete “Kel” and insert --  $K_{el}$  --, therefor.

In column 47, line 12, after “Table 12” insert -- B --.

In column 48, line 33, delete “Cmax” and insert --  $C_{\max}$  --, therefor.

In column 48, line 64, delete “Cmax” and insert --  $C_{\max}$  --, therefor.

In column 48, line 64, delete “AUC<sub>0-t</sub>” and insert --  $AUC_{0-t}$  --, therefor.

In column 48, line 64, delete “AUC $\infty$ ” and insert --  $AUC_{\infty}$  --, therefor.

In column 48, line 66, delete “Cmax” and insert --  $C_{\max}$  --, therefor.

In column 48, line 66, delete “AUC<sub>0-t</sub>” and insert --  $AUC_{0-t}$  --, therefor.

In column 48, line 66, delete “AUC $\infty$ ” and insert --  $AUC_{\infty}$  --, therefor.

In column 49, line 5, delete “K<sub>e</sub>” and insert --  $K_e$  --, therefor.

In column 49, line 63, delete “ng” and insert -- pg --, therefor.

In column 49, line 64, delete “ng” and insert -- pg --, therefor.

In column 49, line 65, delete “ng” and insert -- pg --, therefor.

**CERTIFICATE OF CORRECTION (continued)**

Page 3 of 3

**U.S. Pat. No. 7,981,938 B2**

In column 50, line 66, delete “In-transformed” and insert -- In-transformed --, therefor.

In column 51, line 11, delete “Kel” and insert --  $K_{el}$  --, therefor.

In column 51, line 19, delete “AUC0-t” and insert --  $AUC_{0-t}$  --, therefor.

In column 51, line 19, delete “AUC0-inf” and insert --  $AUC_{0-inf}$  --, therefor.

In column 51, line 20, delete “Cmax” and insert --  $C_{max}$  --, therefor.

In column 51, line 34, delete “AUC0-t” and insert --  $AUC_{0-t}$  --, therefor.

In column 51, line 34, delete “AUC0-inf” and insert --  $AUC_{0-inf}$  --, therefor.

In column 51, line 35, delete “Cmax” and insert --  $C_{max}$  --, therefor.

In column 51, line 64, delete “Kel” and insert --  $K_{el}$  --, therefor.

In column 52, line 19, delete “AUC0-t” and insert --  $AUC_{0-t}$  --, therefor.

In column 52, line 19, delete “AUC0-inf” and insert --  $AUC_{0-inf}$  --, therefor.

In column 52, line 20, delete “Cmax” and insert --  $C_{max}$  --, therefor.

In column 52, line 28, delete “Cmax” and insert --  $C_{max}$  --, therefor.

In column 52, line 30, delete “AUC0-t” and insert --  $AUC_{0-t}$  --, therefor.

In column 52, line 30, delete “AUC0-inf” and insert --  $AUC_{0-inf}$  --, therefor.

In column 52, line 31, delete “Cmax” and insert --  $C_{max}$  --, therefor.

In column 52, line 32, delete “Tmax” and insert --  $T_{max}$  --, therefor.

# EXHIBIT F

US008097655B2

(12) **United States Patent**  
**Davis**

(10) **Patent No.:** **US 8,097,655 B2**  
(45) **Date of Patent:** **\*Jan. 17, 2012**

(54) **METHODS FOR CONCOMITANT  
ADMINISTRATION OF COLCHICINE AND  
MACROLIDE ANTIBIOTICS**

(75) Inventor: **Matthew W. Davis**, Erwinna, PA (US)

(73) Assignee: **Mutual Pharmaceutical Company,  
Inc.**, Philadelphia, PA (US)

(\*) Notice: Subject to any disclaimer, the term of this  
patent is extended or adjusted under 35  
U.S.C. 154(b) by 0 days.

This patent is subject to a terminal dis-  
claimer.

(21) Appl. No.: **13/109,034**

(22) Filed: **May 17, 2011**

(65) **Prior Publication Data**

US 2011/0207825 A1 Aug. 25, 2011

**Related U.S. Application Data**

(63) Continuation of application No. 12/576,355, filed on  
Oct. 9, 2009, which is a continuation-in-part of  
application No. 12/327,258, filed on Dec. 3, 2008, now  
Pat. No. 7,619,004, and a continuation-in-part of  
application No. 12/368,700, filed on Feb. 10, 2009,  
now Pat. No. 7,601,758.

(60) Provisional application No. 61/190,053, filed on Oct.  
15, 2008.

(51) **Int. Cl.**

**A01N 37/18** (2006.01)

**A61K 31/16** (2006.01)

**C07C 233/00** (2006.01)

**C07C 235/00** (2006.01)

**C07C 237/00** (2006.01)

**C07C 239/00** (2006.01)

**C07C 211/00** (2006.01)

**C07C 205/00** (2006.01)

**C07C 207/00** (2006.01)

(52) **U.S. Cl.** ..... **514/629**; 564/123; 564/308; 564/427;  
568/306

(58) **Field of Classification Search** ..... 514/629;  
564/123, 308, 427; 568/306

See application file for complete search history.

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(Continued)

*Primary Examiner* — Sreeni Padmanabhan

*Assistant Examiner* — Kara R McMillian

(74) *Attorney, Agent, or Firm* — Cantor Colburn LLP

(57) **ABSTRACT**

Methods for concomitant administration of colchicine  
together with one or more macrolide antibiotics, e.g.,  
clarithromycin, are disclosed. Such methods reduce the dan-  
gers commonly associated with such concomitant adminis-  
tration and provide additional benefits.

**5 Claims, 2 Drawing Sheets**

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Page 2

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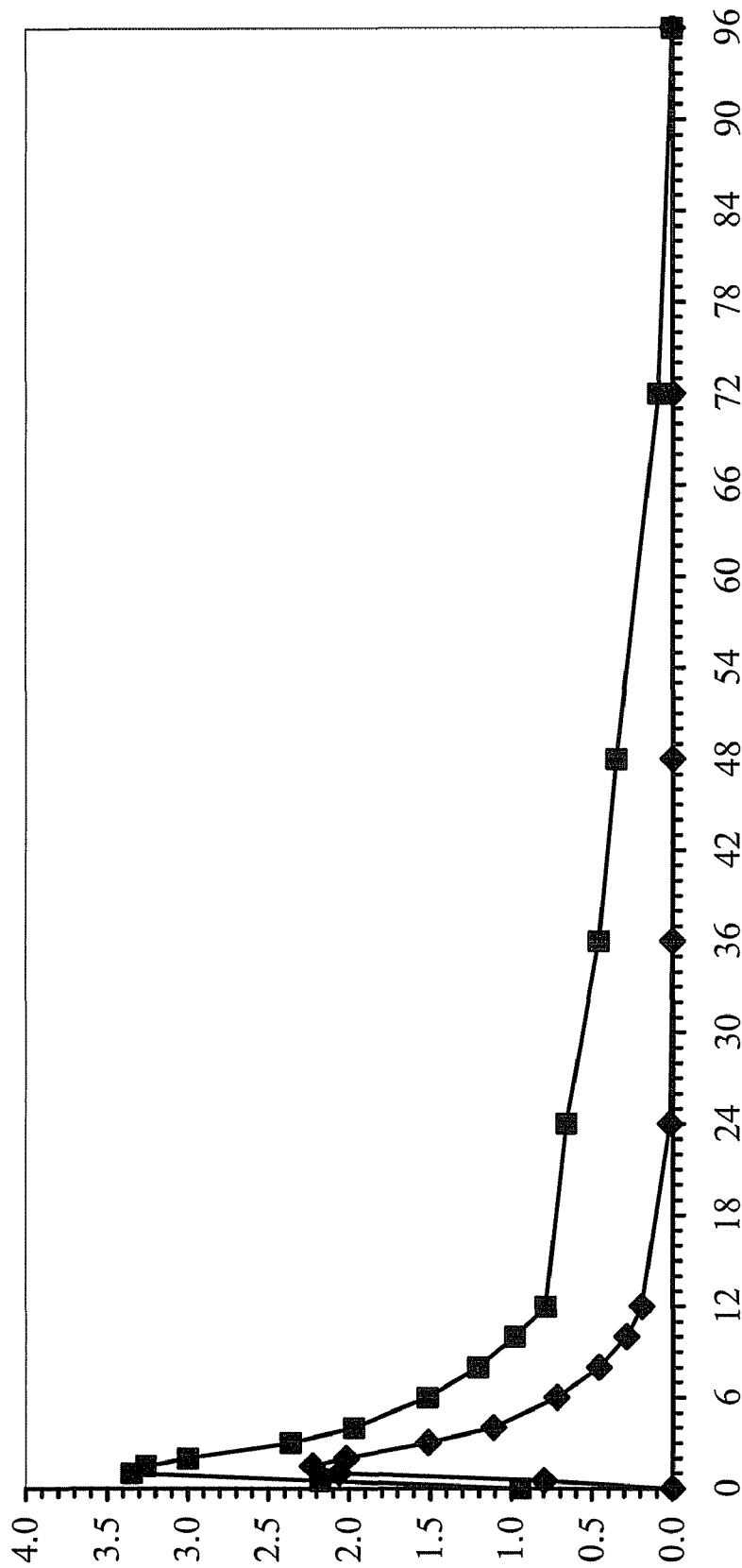
\* cited by examiner

**U.S. Patent**

**Jan. 17, 2012**

**Sheet 1 of 2**

**US 8,097,655 B2**



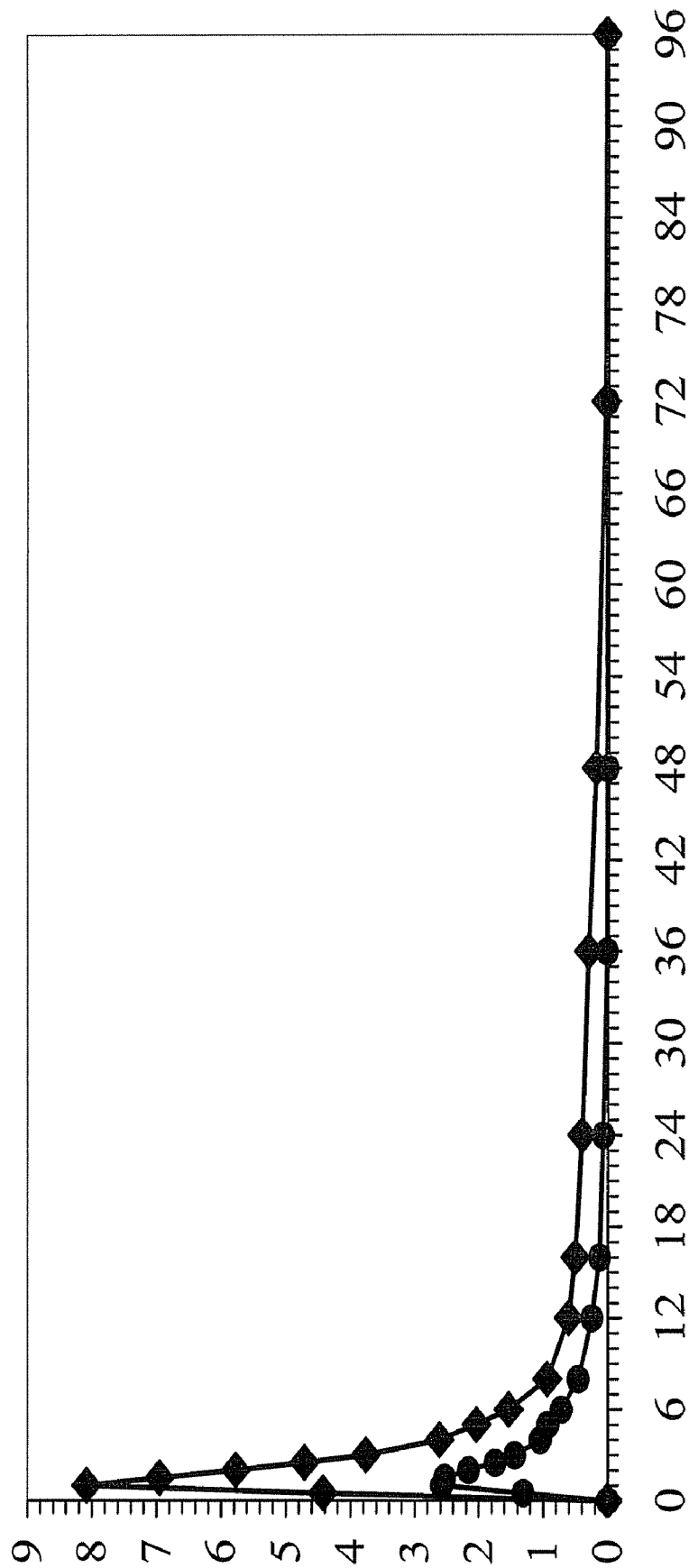
*Fig. 1*

U.S. Patent

Jan. 17, 2012

Sheet 2 of 2

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*Fig. 2*

US 8,097,655 B2

1

# **METHODS FOR CONCOMITANT ADMINISTRATION OF COLCHICINE AND MACROLIDE ANTIBIOTICS**

## **CROSS REFERENCE TO RELATED APPLICATIONS**

This application is a continuation of U.S. application Ser. No. 12/576,355 filed Oct. 9, 2009, which is a continuation-in-part of U.S. patent application Ser. No. 12/327,258 filed on Dec. 3, 2008, now U.S. Pat. No. 7,619,004, issued Nov. 17, 2009, and a continuation of part of U.S. application Ser. No. 12/368,700 filed on Feb. 10, 2009, now U.S. Pat. No. 7,601,758, issued Oct. 13, 2009, all of which claim the benefit of Provisional Patent Application Ser. No. 61/190,053, filed Oct. 15, 2008, and all of which are incorporated herein in their entirety.

## **BACKGROUND**

This application relates to methods allowing for the co-administration of colchicine together with one or more macrolide antibiotics for therapeutic purposes with less danger than is associated with prior methods of administration.

Colchicine:

Colchicine, chemical name (–)-N-[(7S,12aS)-1,2,3,10-tetramethoxy-9-oxo-5,6,7,9-tetrahydrobenzo[a]heptalen-7-yl]-acetamide, is a pale yellow powder soluble in water in 1:25 dilution.

Colchicine is an alkaloid found in extracts of *Colchicum autumnale*, *Gloriosa superba*, and other plants. Among its many biological activities, colchicine blocks microtubule polymerization and arrests cell division. It has adversely affected spermatogenesis in humans and in some animal species under certain conditions.

Colchicine is a microtubule-disrupting agent used in the treatment of gout and other conditions that may be treated, relieved or prevented with anti-inflammatory treatment. Colchicine impairs the motility of granulocytes and can prevent the inflammatory phenomena that initiate an attack (or flare) of gout. Colchicine also inhibits mitosis, thus affecting cells with high turnover such as those in the gastrointestinal tract and bone marrow; therefore, the primary adverse side effects include gastrointestinal upset such as diarrhea and nausea. More serious side effects include morbid complications such as myopathy, neuropathy, bone marrow suppression and drug-induced cytopenia. Particular expressions of these morbid complications may include neuromuscular toxicity with paresthesias, pancytopenia, and seizures.

Colchicine has a low therapeutic index. The margin between an effective dose and a toxic dose of colchicine is much narrower than that of most other widely used drugs. Consequently, actions that result in increased colchicine levels in patients receiving colchicine therapy are particularly dangerous. Co-administration of colchicine to patients along with certain other drugs can have the effect of increasing colchicine levels. Such drug-drug interactions with colchicine have been reported to result in serious morbid complications and, in some cases, death.

Colchicine is rapidly absorbed from the gastrointestinal tract. Peak concentrations occur in 0.5 to 2 hours. The drug and its metabolites are distributed in leukocytes, kidneys, liver, spleen and the intestinal tract. Colchicine is metabolized in the liver and excreted primarily in the feces with 10 to 20% eliminated unchanged in the urine.

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Gout:

Gout (or gouty arthritis) is a disease caused by a build up of uric acid. Such a build up is typically due to an overproduction of uric acid or to a reduced ability of the kidney to excrete uric acid. Gout is more common in certain groups of patients, including adult males, postmenopausal women, and hypertensives. Heavy alcohol use, diabetes, obesity, sickle cell anemia, and kidney disease also increase the risk of developing gout. The condition may also develop in people who take drugs that interfere with uric acid excretion.

In gout, crystals of monosodium urate (a salt of uric acid) are deposited in joints, e.g., on articular cartilage, as well as in and on tendons and surrounding tissues. These deposits correlate with elevated concentrations of uric acid in the blood stream and are believed to provoke the painful inflammatory reaction that occurs in affected tissues. Gout is characterized by excruciating, sudden, unexpected, burning pain, as well as by swelling, redness, warmth, and stiffness in the affected joint. Low-grade fever may also be present. The patient usually suffers from two sources of pain. The patient experiences intense pain whenever an affected joint is flexed. The inflammation of the tissues around the joint also causes the skin to be swollen, tender and sore if it is even slightly touched. For example, a blanket or even the lightest sheet draping over the affected area could cause extreme pain.

A gout flare is a sudden attack of pain in affected joints, especially in the lower extremities, and most commonly in the big toe. In afflicted individuals, the frequency of gout flares typically increases over time. In this fashion, gout progresses from acute gout to chronic gout, which involves repeated episodes of joint pain.

In acute gout flares, symptoms develop suddenly and usually involve only one or a few joints. The big toe, knee, or ankle joints are most often affected. The pain frequently starts during the night and is often described as throbbing, crushing, or excruciating. The joint appears infected, with signs of warmth, redness, and tenderness. Gout flares appear substantially more frequently with more intensive urate-lowering regimens and are a common consequence of therapy with allopurinol. Two randomized clinical trials assessed the efficacy of colchicine 0.6 mg twice a day for the prophylaxis of gout flares in patients with gout initiating treatment with urate lowering therapy. In both trials, treatment with colchicine decreased the frequency of gout flares. Flares of painful joints may go away in several days, but may return from time to time. Subsequent flares usually last longer. Acute gout may progress to chronic gout flares, or may resolve without further attacks.

The chronic appearance of several attacks of gout yearly can lead to joint deformity and limited joint motion. Nodular uric acid deposits, called tophi, may eventually develop in cartilage tissue, tendons, and soft tissues. These tophi are a hallmark of chronic gout, which usually develop only after a patient has suffered from the disease for many years. Deposits of monosodium urate can also occur in the kidneys of gout sufferers, potentially leading to chronic kidney failure.

Use of Colchicine to Treat Gout:

Colchicine can reduce pain in attacks of acute gout flares and also can be used beneficially for treating adults for prophylaxis of gout flares. Although its exact mode of action in the relief of gout is not completely understood, colchicine is known to decrease the inflammatory response to urate crystal deposition by inhibiting migration of leukocytes, to interfere with urate deposition by decreasing lactic acid production by leukocytes, to interfere with kinin formation and to diminish phagocytosis and subsequent inflammatory responses.

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The anti-inflammatory effect of colchicine is relatively selective for gouty arthritis. However, other types of arthritis occasionally respond. It is neither an analgesic nor a uricosuric and will not prevent progression of acute gout to chronic gout. It does have a prophylactic, suppressive effect that helps to reduce the incidence of acute attacks as well as to relieve the residual pain and mild discomfort that patients with gout occasionally experience between attacks.

#### Macrolide Antibiotics:

Macrolide compounds are natural products and natural product derivatives characterized by the presence of a macrocyclic (large) lactone ring known as a macrolide ring. The macrolide antibiotics are important therapeutic agents. Commercially available macrolide antibiotics include azithromycin, clarithromycin, dirithromycin, erythromycin, and roxithromycin.

Clarithromycin is a semi-synthetic macrolide antibiotic with in vitro activity against a variety of aerobic and anaerobic gram-positive and gram-negative microorganisms, as well as most *Mycobacterium avium* complex (MAC) microorganisms. The drug is believed to exert its antibacterial action by binding to 50S ribosomal subunits in susceptible microorganisms, resulting in inhibition of protein synthesis.

Clarithromycin is indicated in the treatment of mild to moderate infections in adults and children caused by susceptible strains of microorganisms, such as *Legionella pneumophila*, *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Neisseria gonorrhoeae*. Clarithromycin is also used to treat pharyngitis (tonsillitis), sinusitis, bronchitis, community-acquired pneumonia, uncomplicated skin infections, and disseminated mycobacterial infections. The usual adult dose is 250 or 500 mg every 12 hours (500 or 100 mg per day) for 7 to 14 days, taken without regard to food.

Clarithromycin is rapidly absorbed from the gastrointestinal tract following oral administration, with an absolute bioavailability of approximately 50%. Peak plasma concentrations with single doses are reached within 2 to 3 hours and steady-state plasma concentrations are reached within 3 to 4 days. Food slightly delays the onset of absorption and time to peak concentration and increases the peak concentration by about 24%, but does not affect the extent of exposure. Clarithromycin distributes readily into body tissues and fluids and is not highly bound to plasma proteins (65 to 75%).

#### Cytochrome p450 (CYP) Enzymes:

CYP enzymes are agents of drug metabolism that are found in the liver, the gastrointestinal tract and other locations in the body. CYP enzymes occur in a variety of closely related proteins referred to as isozymes. Some of these that have been identified as important in drug metabolism are CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, and CYP3A5. Different CYP isozymes may preferentially metabolize different drugs. For example, phenytoin and fosphenytoin have been reported to be preferentially metabolized by CYP2C9, CYP2C19, and CYP3A4, while CYP2D6 has been reported to be responsible for the metabolism of many psychotherapeutic agents, such as thioridazine.

#### CYP Isozymes and Drug-Drug Interactions:

Examples of CYP-mediated drug-drug interactions include those involving CYP1A2 and CYP2E1 isozymes, which have been reported to be involved in drug-drug interactions involving theophylline, and those involving CYP2C9, CYP1A2, and CYP2C19, which have been reported to be involved in drug-drug interactions involving warfarin.

The 3A family of CYP isozymes, particularly CYP3A4, is also known to be involved in many clinically significant drug-drug interactions, including those involving colchicine and

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macrolide antibiotics, as well as those involving non-sedating antihistamines and cisapride. CYP3A5 shares very similar protein structure, function and substrate specificity with CYP3A4. The CYP3A5\*3 allele is a gene variant that does not express CYP3A5 enzyme. As a result of this genetic variation, about half of African-American subjects and 70-90% of Caucasian subjects do not express CYP3A5, while expression is more common in other ethnic groups.

While drugs are often targets of CYP-mediated metabolism, some may also alter the expression and activity of such enzymes, thus impacting the metabolism of other drugs.

Colchicine is both a target of and a modulator of CYP isozymes. The biotransformation of colchicine in human liver microsomes involves formation of 3-demethylcolchicine and 2-demethylcolchicine. As shown by experiments using antibodies against CYP3A4 and experiments using chemical inhibition of CYP3A4, this transformation is correlated with (and thus apparently mediated by) CYP3A4 activity. CYP2A6, CYP2C9, CYP2C19, CYP2D6, and CYP2E1 do not appear to catalyze this biotransformation.

Studies on the effect of colchicine on expression of selected CYP isozymes in primary cultures of human hepatocytes have been reported. Dvorak et al. (Acta Univ. Palacki. Olomuc., Fac. Med. (2000) 143:47-50) provided preliminary data on the effect of colchicine and several of its derivatives on protein levels of CYP1A2, CYP2A6, CYP2C9/19, CYP2E1, and CYP3A4 as assessed by immunoblotting. Colchicine caused an increase in CYP2E1 protein levels and appeared to decrease protein levels of CYP1A2, CYP2C9/19, and CYP3A4, with 10  $\mu$ M colchicine causing a greater reduction in each isozyme than 1  $\mu$ M colchicine. The 3-demethylcolchicine metabolite was reported to cause a decrease in protein for CYP1A2, CYP2C9/19, CYP2E1, and CYP3A4. The levels of CYP2A6 appeared unaffected by colchicine or any of the tested metabolites. In a more complete report on expression of CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2E1, and CYP3A4, Dvorak et al. (Toxicology in Vitro (2002) 16:219-227) concluded that CYP1A2 protein content in 1  $\mu$ M colchicine treated cells was not different from that in control cells, while the inducer TCDD increased the level of CYP1A2 protein by an average of three-fold. The levels of CYP2A6 protein were apparently unaffected by colchicine, while enzyme activities of CYP3A4 and CYP2C9 were significantly decreased by colchicine and activity of CYP2E1 was not affected. Northern blots showed that colchicine suppressed CYP2C9 mRNA levels by about 20% and did not alter CYP3A4 mRNA levels as compared to control cells. A subsequent study by Dvorak et al. (Mol. Pharmacol. (2003) 64:160-169) showed that colchicine decreased both basal and rifampicin-inducible and phenobarbital-inducible expression of CYP2B6, CYP2C8/9, and CYP3A4.

Like colchicine, clarithromycin is a target of metabolism by CYP3A isozymes. In non-fasting healthy human subjects, the elimination half-life of clarithromycin is about 3 to 4 hours with 250 mg administered every 12 hours, but increases to 5 to 7 hours with 500 mg administered every 8 to 12 hours. Approximately 20% and 30% of the dose, respectively, is excreted as unchanged drug in urine following oral administration of 250 and 500 mg clarithromycin given every 12 hours. Approximately 10 to 15% of the dose is excreted in urine as 14-hydroxyclearithromycin, an active metabolite of clarithromycin with substantial antibacterial activity. About 40% of an oral clarithromycin dose is excreted in feces.

Clarithromycin is also a potent inhibitor of CYP3A isozymes, as are other macrolide antibiotics. This inhibition is not rapidly reversible. Due to the limited reversibility of the inhibition of CYP3A isozymes by clarithromycin, CYP3A

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activity may not return to normal after a course of treatment with clarithromycin until the body produces adequate amounts of CYP3A isozymes to replace those irreversibly inhibited by the clarithromycin. Thus, it may take one to two weeks for CYP3A metabolic activity to return to normal following treatment with clarithromycin or other macrolide antibiotics.

P-glycoprotein (Pgp) is an ATP-dependent cell surface transporter molecule. Pgp actively pumps certain compounds, notably including drugs such as colchicine, out of cells. Pgp is encoded by the Adenosine triphosphate-binding cassette subfamily B member 1 (ABCB 1) gene, also referred to as the multiple drug resistance 1 gene (MDR1).

Clarithromycin is an inhibitor of Pgp, as are other macrolide antibiotics. In vitro, agents that inhibit CYP 3A4 typically also inhibit Pgp, and the magnitude of Pgp inhibition in vitro generally trends proportionally with magnitude of CYP 3A4 inhibition. However, equipotent CYP 3A4 inhibitors can exhibit different degrees of Pgp inhibition.

Thus clarithromycin and other macrolide antibiotics, in addition to inhibiting the metabolic breakdown of colchicine by inhibiting CYP 3A4 isozymes, can block a mechanism by which colchicine is pumped out of cells. Both the inhibition of colchicine breakdown by CYP 3A4 and the inhibition of the pumping of colchicine out of cells by Pgp have the effect of increasing the intracellular levels of colchicine.

Since colchicine acts intracellularly, the combined effects of CYP 3A4 inhibition and Pgp inhibition by clarithromycin (and related macrolide antibiotics) can cause colchicine toxicity in patients taking what would be a safe dose of colchicine in the absence of concomitant macrolide antibiotic administration.

Drug-drug interactions, such as the enhancement of colchicine toxicity by macrolide antibiotics, present a health risk to patients and a medical challenge for all medical care workers. Various studies of adverse reactions from exposure to multiple drugs have found that 6.5-23% of the adverse reactions result from drug-drug interactions. Unfortunately, each year a number of deaths occur as the direct result of patients adding a concomitant prescription pharmaceutical product to their existing medication regimen.

With regard to co-administration of colchicine with clarithromycin and other macrolide antibiotics, warnings have recently been published urging caution, or arguing that the two drugs should not be co-administered. For example, on Jul. 5, 2006 the US Food and Drug Administration (the FDA) approved safety labeling changes for clarithromycin tablets, extended-release tablets, and oral suspension to warn of the risk for increased exposure to colchicine in patients receiving both drugs. The Warnings section of the prescribing information for clarithromycin now includes the following statement: "There have been post-marketing reports of colchicine toxicity with concomitant use of clarithromycin and colchicine, especially in the elderly, some of which occurred in patients with renal insufficiency. Deaths have been reported in some such patients." In addition, the following was added to the Precautions section of the prescribing information: "[c]olchicine is a substrate for both CYP3A and the efflux transporter, P-glycoprotein (Pgp). Clarithromycin and other macrolides are known to inhibit CYP3A and Pgp. When clarithromycin and colchicine are administered together, inhibition of Pgp and/or CYP3A by clarithromycin may lead to increased exposure to colchicine. Patients should be monitored for clinical symptoms of colchicine toxicity."

A 2006 report entitled "Life-threatening Colchicine Drug Interactions" cautioned that "[c]olchicine should not be used with clarithromycin or erythromycin, and given the potential

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for fatal outcomes, it would be prudent to avoid all PGP inhibitors with colchicine" (Horn, J. R. and Hansten, P. D., Pharmacy Times, May 2006, p. 111).

More recently, a publication in May, 2008 ended with the conclusion that "[t]he combined prescription of clarithromycin or other CYP3A4 inhibitors and colchicine should be avoided." Van der Velden, et al., (Neth. J. Med. 2008 May; 66(5):204-6).

There accordingly remains a need in the art for improved methods for administering colchicine to patients who are concomitantly being treated with macrolide antibiotics so as to reduce the occurrence of dangerous colchicine toxicity. The present disclosure addresses this need and provides further advantages.

#### BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows mean colchicine plasma concentrations following administration of single and multiple oral doses of colchicine 0.6 mg in healthy adults, N=13, Y axis=colchicine concentration, ng/mL, X axis=time in hours, ◆=day 1, □=day 25. See Example 1.

FIG. 2 shows a pharmacokinetic profile comparison of single-dose colchicine (0.6 mg, alone) and single-dose colchicine (0.6 mg) co-administered with steady-state clarithromycin in healthy adults, Y axis=colchicine concentration, ng/mL, X axis=time in hours, N=23, ○=day 1, ◆=day 29. See Example 2.

#### SUMMARY

Disclosed herein are methods for more safely administering colchicine concomitantly with administration of macrolide antibiotics such as clarithromycin or erythromycin. It has now been discovered that certain reduced or limited colchicine dosages, when administered with concomitantly administered recommended dosage amounts of macrolide antibiotics, certain "colchicine plus macrolide" dosing regimens, achieve plasma colchicine levels that are therapeutically effective, but are not significantly higher, and therefore not significantly more toxic, than plasma levels achieved by administration of manufacturers' recommended colchicine dosage amounts in the absence of concomitant macrolide antibiotic administration. Thus, in spite of recent published warnings that the two should not be concomitantly administered, colchicine and macrolide antibiotics can be administered concomitantly without undue hazard when colchicine is administered as disclosed herein.

In one embodiment, colchicine treatment is administered to a patient in suffering from a condition treatable with colchicine, and the patient is concomitantly receiving administration of a macrolide antibiotic to treat an infection. The colchicine therapy may involve either palliative or prophylactic treatment, or both.

In one embodiment, colchicine is employed in the prophylaxis of gout flares in a human individual, that is, to prevent gout flares. Such treatment can also be referred to as chronic treatment, meaning long-term treatment to reduce the occurrence of gout flares. In one embodiment, the method comprises determining a first colchicine dosage amount adapted for daily oral administration to the gout patient to prevent gout flares in the absence of concomitant administration of clarithromycin or erythromycin, determining a second colchicine dosage amount that is a 50% to 75% reduction of the first colchicine dosage amount, and orally administering the second colchicine dosage amount to the gout patient who is concomitantly receiving administration of clarithromycin

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or erythromycin. The second colchicine dosage amount is administered to the patient in one or more doses one or more times per day every day, or double the second colchicine dosage amount is administered to the patient in one or more doses per day every other day.

In certain embodiments, in this method, the 50% to 75% reduction comprises one or more of 1) reducing the number of doses of colchicine administered per day, 2) reducing the amount of colchicine administered per dose, and 3) reducing the administration of colchicine from administration every day to administration every other day. For example, in this method, the 50% to 75% reduction may comprise reducing both the number of doses of colchicine administered per day and the amount of colchicine administered per dose.

In other aspects of these embodiments, one or more (where not mutually exclusive) of the following applies: 1) the patient is administered each dose of colchicine as one 0.6 mg colchicine tablet or as one half of a 0.6 mg colchicine tablet, 2) the patient is an adult, 3) the adult patient is less than 70 years old, 4) the patient is receiving concomitant administration of clarithromycin, 6) the second colchicine dosage amount is a one-half reduction of the first colchicine dosage amount, 7) the second colchicine dosage amount is a two-thirds reduction of the first colchicine dosage amount, 8) the second colchicine dosage amount is a three-quarters reduction of the first colchicine dosage amount, 9) the first colchicine dosage amount is about 1.2 mg per day and the second colchicine dosage amount is about 0.3 mg per day, 10) the first colchicine dosage amount is about 0.6 mg per day and the second colchicine dosage amount is about 0.15 mg per day.

In aspects of these embodiments, the second colchicine dosage amount of about 0.3 mg per day is administered as one half of a 0.6 mg colchicine tablet once a day every day, and the second colchicine dosage amount of about 0.15 mg per day is administered as one half of a 0.6 mg colchicine tablet once a day every other day.

In one embodiment, a method of using colchicine for prophylactic treatment of gout flares in a human gout patient so as to reduce the occurrence of colchicine toxicity when said patient is receiving concomitant administration of clarithromycin or erythromycin, comprises: orally administering a second colchicine daily dosage amount for prophylactic treatment of gout flares to the human gout patient who is concomitantly receiving administration of clarithromycin or erythromycin, wherein the second colchicine daily dosage amount is a 50 to 75% reduction of a first colchicine daily dosage amount suitable for daily oral administration for the prophylactic treatment of gout flares in the absence of concomitant administration of clarithromycin or erythromycin, wherein concomitant administration of clarithromycin or erythromycin is administration within 1 to 2 days of orally administering the second colchicine dosage amount, and wherein the first colchicine daily dosage amount is 1.2 mg administered as two 0.6 mg doses per day, or the first colchicine daily dosage amount is 0.6 mg per day.

In another embodiment, a method of using colchicine for prophylactic treatment of gout flares in a human gout patient so as to reduce the occurrence of colchicine toxicity when said patient is receiving concomitant administration of clarithromycin or erythromycin, comprises: orally administering a second colchicine daily dosage amount for prophylactic treatment of gout flares to the human gout patient who is concomitantly receiving administration of clarithromycin or erythromycin, wherein the second colchicine daily dosage amount is a 75% reduction of a first colchicine daily dosage amount suitable for daily oral administration for the prophylactic treatment of gout flares in the absence of concomitant

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administration of clarithromycin or erythromycin, wherein concomitant administration of clarithromycin or erythromycin is administration within 1 to 2 days of orally administering the second colchicine dosage amount. In certain embodiments, the first colchicine daily dosage amount is 1.2 mg administered as two 0.6 mg doses per day, or the first colchicine daily dosage amount is 0.6 mg per day.

In another embodiment, a method of using colchicine for prophylactic treatment of gout flares in an adult human gout patient so as to reduce the occurrence of colchicine toxicity when said patient is receiving concomitant administration of clarithromycin or erythromycin comprises administering a reduced colchicine daily dosage amount to the patient for prophylactic treatment of gout flares, wherein the reduced colchicine daily dosage amount is 50-75% of a manufacturers' recommended colchicine daily dosage amount for the prophylactic treatment of gout flares in the absence of concomitant clarithromycin or erythromycin administration, wherein concomitant administration of clarithromycin or erythromycin is administration within 1 to 2 days of orally administering the second colchicine dosage amount. In certain embodiments, the manufacturers' recommended colchicine daily dosage amount for the prophylactic treatment of gout flares in the absence of concomitant clarithromycin or erythromycin administration is 1.2 mg/day or 0.6 mg/day.

In another embodiment, a method of using colchicine for prophylactic treatment of gout flares in an adult human gout patient so as to reduce the occurrence of colchicine toxicity when said patient is receiving concomitant administration of clarithromycin or erythromycin comprises administering a reduced colchicine daily dosage amount to the patient for prophylactic treatment of gout flares, wherein the reduced colchicine daily dosage amount is 75% of a manufacturers' recommended colchicine daily dosage amount for the prophylactic treatment of gout flares in the absence of concomitant clarithromycin or erythromycin administration, wherein concomitant administration of clarithromycin or erythromycin is administration within 1 to 2 days of orally administering the second colchicine dosage amount.

In one embodiment, the daily colchicine is coadministered with a urate-lowering drug such as febuxostat or allopurinol. Daily dosage amounts of febuxostat are typically 40 mg or 80 mg once daily. Daily dosage amounts of allopurinol are 200 to 300 mg per day for patients with mild gout and 400 to 600 mg per day for those with moderately severe tophaceous gout. The appropriate dosage amount may be administered in divided doses or as a single equivalent dose with the 300 mg tablet. Dosage requirements in excess of 300 mg should be administered in divided doses. The minimal effective dosage amount is 100 to 200 mg daily and the maximal recommended dosage amount is 800 mg daily. To reduce the possibility of flare-up of acute gouty attacks, it is recommended that the patient start with a low dosage amount of allopurinol (100 mg daily) and increase at weekly intervals by 100 mg until a serum uric acid level of 6 mg/dL or less is attained but without exceeding the maximal recommended dosage amount.

In yet another embodiment, a method of using colchicine for prophylactic treatment of gout flares in a human gout patient that is also receiving treatment with urate-lowering therapy so as to reduce the occurrence of colchicine toxicity when said patient is receiving concomitant administration of clarithromycin or erythromycin, comprises: orally administering a second colchicine daily dosage amount for prophylactic treatment of gout flares to the human gout patient who is concomitantly receiving administration of clarithromycin or erythromycin, wherein the second colchicine daily dosage

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amount is a 75% reduction of a first colchicine daily dosage amount suitable for daily oral administration for the prophylactic treatment of gout flares in the absence of concomitant administration of clarithromycin or erythromycin, wherein concomitant administration of clarithromycin or erythromycin is administration within 1 to 2 days of orally administering the second colchicine dosage amount. In certain embodiments, the first colchicine daily dosage amount is 1.2 mg administered as two 0.6 mg doses per day, or the first colchicine daily dosage amount is 0.6 mg per day. In certain embodiments, the urate lowering therapy is allopurinol or febuxostat.

In another embodiment, colchicine is used for the treatment of acute gout, that is, treatment of gout flares. In one embodiment, the method comprises determining a first colchicine dosage amount adapted for oral administration to the gout patient to treat gout flares in the absence of concomitant administration of clarithromycin or erythromycin, determining a second colchicine dosage amount that is a 50% to 75% reduction, preferably a two-thirds or three quarters reduction, of the first colchicine dosage amount, and orally administering the second colchicine dosage amount to the gout patient who is concomitantly receiving administration of clarithromycin or erythromycin. In one embodiment, the colchicine administration is not repeated for at least three days.

In certain embodiments, the 50% to 75% reduction comprises one or more of 1) reducing the number of doses of colchicine administered (e.g., per day), 2) reducing the amount of colchicine administered per dose (i.e., reducing the size of at least one colchicine dose), and 3) reducing the administration of colchicine from administration every day to administration every other day. For example, in this method, the 50% to 75% reduction may comprise reducing both the number of doses of colchicine administered per day and the amount of colchicine administered per dose. In one embodiment, the colchicine administration is not repeated for at least three days.

In other aspects of these embodiments, one or more (where not mutually exclusive) of the following apply: 1) the patient is administered each dose of colchicine as one 0.6 mg colchicine tablet or as one half of a 0.6 mg colchicine tablet (e.g. one half a scored 0.6 mg colchicine tablet), 2) the patient is an adult, 3) the adult patient is less than 70 years old, 4) the patient is receiving concomitant administration of clarithromycin, 5) the second colchicine dosage amount is about a one-half reduction of the first colchicine dosage amount, 6) the second colchicine dosage amount is about a two-thirds reduction of the first colchicine dosage amount, 7) the second colchicine dosage amount is about a three-quarters reduction of the first colchicine dosage amount, 8) the first colchicine dosage amount is about 1.8 mg per day and the second colchicine dosage amount is about 0.6 mg per day, 9) the second colchicine dosage amount is a single dose of about 0.6 mg, and after administration of the single dose ingestion of colchicine is stopped until a subsequent gout flare occurs, 10) the second colchicine dosage amount is a single dose of about 0.6 mg of colchicine, and after administration of the single dose ingestion of colchicine is not repeated within a 3-day period.

In an additional embodiment, the first colchicine dosage amount is about 1.8 mg per day and the second colchicine dosage amount is a single 0.6 mg dose, and preferably ingestion of colchicine is not repeated for at least three days after the single dose is administered.

In another embodiment, a method of using colchicine to treat a gout flare in a human patient who is receiving concomitant administration of clarithromycin or erythromycin

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comprises determining a first colchicine dosage amount adapted for oral administration to the patient to treat a gout flare in the absence of concomitant administration of clarithromycin or erythromycin, determining a second colchicine dosage amount that is a 50-75% reduction of the first colchicine dosage amount, and orally administering the second colchicine dosage amount to the patient who is experiencing a gout flare and is concomitantly receiving administration of clarithromycin or erythromycin, wherein concomitant administration of clarithromycin or erythromycin is administration within 1 to 2 days of orally administering the second colchicine dosage amount, and not repeating colchicine administration for at least three days.

In another embodiment, a method of using colchicine to treat a gout flare in a human patient who is receiving concomitant administration of clarithromycin or erythromycin comprises determining a first colchicine dosage amount adapted for oral administration to the patient to treat a gout flare in the absence of concomitant administration of clarithromycin or erythromycin, determining a second colchicine dosage amount that is about a two thirds reduction of the first colchicine dosage amount, and orally administering the second colchicine dosage amount to the patient who is experiencing a gout flare and is concomitantly receiving administration of clarithromycin or erythromycin, wherein concomitant administration of clarithromycin or erythromycin is administration within 1 to 2 days of orally administering the second colchicine dosage amount, and not repeating colchicine administration for at least three days.

In another embodiment, a method of using colchicine to treat a gout flare in an adult human gout patient so as to reduce the occurrence of colchicine toxicity when said patient is receiving concomitant administration of clarithromycin or erythromycin comprises administering a reduced colchicine dosage amount to the patient to treat gout flares, wherein the reduced colchicine dosage amount is about 50% to about 75% of a manufacturer's recommended colchicine dosage amount in the absence of concomitant clarithromycin or erythromycin administration, and not repeating colchicine administration for at least three days, wherein concomitant administration of clarithromycin or erythromycin is administration within 1 to 2 days of orally administering the second colchicine dosage amount.

In a one embodiment, the patient is administered the colchicine according to a colchicine dosing regimen of a single starting colchicine dose of no more than about 0.6 mg colchicine, followed by either no additional colchicine doses within about 12, 24, 48, or 72 hours, or followed by at least one additional colchicine dose within 12 hours and no more frequently than once every hour (e.g., every 3, 4, 6, 8, or 12 hours). In this embodiment, each additional colchicine dose is no greater than about 0.3 mg and the patient may be an adult patient or a pediatric patient. In one embodiment, the starting colchicine dose is about 0.6 mg or about 0.3 mg, and each additional colchicine dose is about 0.3 mg. When additional doses are administered, it is preferred that only two, three, or four additional colchicine doses are administered within about 24 hours. In another embodiment, the patient is an adult patient and the starting colchicine dose is about 0.6 mg and each additional colchicine dose, if any, is about 0.3 mg. In one embodiment only three additional colchicine doses are administered within about 24 hours.

In another embodiment, colchicine is administered to a patient suffering from a condition treatable with colchicine, and the concomitant macrolide antibiotic is administered concurrently, or the patient has recently completed a dosing regimen of a macrolide antibiotic to treat an infection, and the

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patient is (immediately or within a period of two weeks, preferably three days, more preferably within 48 hours or 24 hours after completion of the macrolide antibiotic dosing regimen) administered a single dose of no more than about 0.6 mg of colchicine, preferably 0.3 mg or 0.6 mg of colchicine. For example, the starting colchicine dose is about 0.6 mg and only one additional colchicine dose is administered within about 24 hours and the additional colchicine dose is about 0.6 mg.

A preferred antibiotic for use in the disclosed methods is one that is an inhibitor of either or both of CYP3A and P-glycoprotein, preferably both. In certain embodiments, the antibiotic is dirithromycin, erythromycin, roxithromycin, or more preferably, clarithromycin or erythromycin. The clarithromycin may be administered to the patient at a dosage amount of about 500 mg daily and the colchicine dosing regimen is one about 0.6 mg colchicine dose to start, followed by 0, 1, 2, 3, or 4 additional colchicine doses of about 0.6 mg every 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 hours (e.g., every 2, 3, 4, 5, or 6 hours) after the preceding colchicine dose. Alternatively, the clarithromycin may be administered to the patient at a dosage amount of about 1000 mg daily and the colchicine dosing regimen is one about 0.3 mg colchicine dose to start, followed by 0, 1, 2, 3, or 4 additional colchicine doses of about 0.3 mg each every 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 hours (e.g., every 3, 4, 5, or 6 hours) after the preceding colchicine dose. In a preferred regimen for treatment of acute gout flares, ingestion of colchicine is continued until a total of no more than about 1.2, 1.4, 1.6, 1.8, 2, or 2.4 mg of colchicine has been ingested, after which ingestion of colchicine is stopped until a subsequent acute gout flare occurs. In still another preferred regimen, clarithromycin may be administered to a patient, e.g., at a dosage amount of about 250 mg B.I.D. for a period of about 7 to 10 days, and the colchicine dosing regimen is administered to the patient upon completion of the clarithromycin dosing regimen, wherein the colchicine dosing regimen consists of the administration of no more than one dose of no more than 0.6 mg of colchicine. In one embodiment, the colchicine is administered as a dosage form of 0.6 mg (e.g., one 0.6 mg colchicine tablet), or 0.3 mg (e.g., one half of a 0.6 mg tablet) of colchicine and administration of the dosage form is not repeated within a period of at least about two days, preferably at least about three days.

In these and other embodiments, the colchicine-responsive condition is gout (e.g. a gout flare in a chronic gout sufferer), familial Mediterranean fever (FMF), thrombocytopenic purpura, pericarditis, scleroderma, or Behcet's disease. The gout may be an acute gout flare or chronic gout. For gout, the dosing regimen is generally continued until a total of no more than 2.4 mg of colchicine has been ingested, after which ingestion of colchicine is stopped until a subsequent gout flare occurs.

Another embodiment comprises administering colchicine to a patient also taking clarithromycin, or having completed treatment with clarithromycin within the prior 14 days, the patient being administered a single dosage amount of about 0.6 mg or about 0.3 mg of colchicine to treat a gout flare, which administration is not repeated within any 3-day period.

In another aspect, herein disclosed is a method for increasing the blood plasma levels of colchicine in a patient to whom colchicine is being administered to treat or prevent a colchicine-responsive condition. This method comprises the concomitant dosing of the patient with a sufficient amount of a macrolide antibiotic to increase the  $C_{max}$  of colchicine by about 167% to 200%, or to increase the AUC of colchicine in the patient by about 240% to 250%, or to increase the plasma half-life of colchicine by about 233%, or to decrease the

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clearance of colchicine by about 75%, compared to the  $C_{max}$ , AUC, plasma half-life, or clearance in the same or a matched patient when not being administered a concomitant macrolide antibiotic. In a one embodiment, the patient is being administered no more than three hourly doses of about 0.6 mg of colchicine or less, the macrolide antibiotic is clarithromycin, and the amount of macrolide antibiotic is from about 500 mg to about 1000 mg, with about 500 mg being preferred.

In another aspect, herein disclosed are methods for using colchicine which methods involve the use of pharmacy management systems.

In one aspect one such method comprises a pharmacy receiving a prescription for colchicine for a patient who is suffering from gout (e.g., acute gout flares or chronic gout) and who is concomitantly being treated with a macrolide antibiotic that is an inhibitor of CYP3A and P-glycoprotein, followed by the pharmacy dispensing colchicine in response to receipt of the prescription, wherein the dispensing is preceded by entry into a first computer readable storage medium, in functional communication with a computer, of a unique patient identifier for said patient and at least one drug identifier for colchicine linked to the patient identifier so as to indicate that colchicine is to be administered to the patient. The computer is programmed to issue a drug-drug interaction alert when the at least one drug identifier for colchicine is entered linked to the patient identifier so as to indicate that colchicine is to be administered to the patient and when the patient identifier is also linked to an identifier indicating that a macrolide antibiotic that is an inhibitor of CYP3A or P-glycoprotein is being concomitantly administered to the patient. Upon entry of the at least one drug identifier for colchicine linked to the patient identifier, a drug-drug interaction alert is issued to one or more of a pharmacy technician, a pharmacist, or a pharmacy customer obtaining the colchicine, said alert indicating that a macrolide antibiotic is being concomitantly administered to the patient and that prior to the colchicine being dispensed, the colchicine dosing regimen must be reviewed and, if necessary adjusted, so that when the colchicine is delivered to the pharmacy customer obtaining the colchicine it is delivered along with instructions for the colchicine to be taken in accordance with a dosing regimen of no more than one about 0.6 mg colchicine dose to start (e.g., following the onset of the acute gout attack or the first sign of a gout flare) followed by either: no additional colchicine doses within about 12, 24, 48, or 72 hours, or at least one additional colchicine dose within about 12 hours and no more frequently than once every hour and wherein each additional colchicine dose is no greater than about 0.6 mg, and wherein the patient ingests the colchicine as instructed.

The drug-drug interaction alert may be issued as one or both of a written warning on a display screen of the pharmacy management computer system, and a printed warning. The printed warning may be attached to or packaged with the dispensed prescription.

In one aspect, the identifier indicating that a macrolide antibiotic is being concomitantly administered to the patient is an identifier indicating that the macrolide antibiotic is clarithromycin and is linked to at least one further identifier indicating that the clarithromycin is prescribed so that 500 mg of clarithromycin is to be ingested by the patient daily, in which case the dosing regimen for colchicine is preferably one about 0.6 mg colchicine dose to start, optionally followed by additional colchicine doses, e.g., 0, 1, 2, 3, or 4 additional colchicine doses within 24 hours of about 0.3 mg ingested every 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 hours (e.g., every 2, 3, 4, 5, or 6 hours) after the preceding colchicine dose. In another embodiment, the identifier indicating that a mac-

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rolide antibiotic is being concomitantly administered to the patient is an identifier indicating that the macrolide antibiotic is clarithromycin is linked to at least one further identifier, entered into a second computer readable storage medium in functional communication with a computer, the second storage medium being the same as or different from the first storage medium, and the further identifier indicating that the clarithromycin is prescribed so that about 500 mg of clarithromycin is to be ingested by the patient daily, in which case the colchicine dosing regimen is (preferably) one about 0.6 mg colchicine dose to start, followed by an about 0.3 mg colchicine dose ingested every 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 hours (e.g., every six to eight hours) after the preceding colchicine dose.

In yet another aspect, the identifier indicating that a macrolide antibiotic is being concomitantly administered to the patient is an identifier indicating that the macrolide antibiotic is clarithromycin and is linked to at least one further identifier, entered into a second computer readable storage medium in functional communication with a computer, the second storage medium being the same as or different from the first storage medium, and the further identifier indicating that the clarithromycin is prescribed so that about 1000 mg of clarithromycin is to be ingested by the patient daily and the dosing regimen is one about 0.3 mg colchicine dose to start, followed by an about 0.3 mg colchicine dose ingested every 2, 3, 4, 5, 6, 7, or 8 hours (e.g., every eight to twelve hours) after the preceding colchicine dose.

One dosing regimen calls for ingestion of colchicine to be continued until a total of no more than 1.2 mg or 2.4 mg of colchicine has been ingested, after which ingestion of colchicine is to be stopped, e.g., for at least 2, 3, 4, 5, 6, or 7 days, or until a subsequent acute gout flare, or the first sign of a subsequent gout flare, occurs.

Also disclosed herein is a dosage amount adjustment method for administering colchicine to a patient to treat a medical condition, the patient concomitantly suffering from an infection amenable to treatment with a macrolide antibiotic. The method comprises determining a first, a second, and a subsequent monotherapy colchicine dosage amount and a colchicine treatment schedule; and determining an antibiotic dosage amount and an antibiotic treatment schedule; and administering the macrolide antibiotic to the patient at the antibiotic dosage amount according to the antibiotic treatment schedule while concomitantly administering colchicine to the patient according to the colchicine treatment schedule at a first, a second, and a subsequent polytherapy colchicine dosage amount, each of which is a fraction of each of the corresponding first, second, and subsequent monotherapy colchicine dosage amounts, the fraction being less than or equal to about  $\frac{2}{3}$ .

An alternate embodiment of this method comprises determining a monotherapy colchicine dosage amount and a colchicine treatment schedule, each adapted so that, when colchicine is administered to the patient in the absence of concomitant administration of the antibiotic at the monotherapy colchicine dosage amount according to the colchicine treatment schedule, a therapeutic circulating plasma level of colchicine is predicted to be achieved in the patient that is safe and effective to treat the condition in the patient while posing an acceptable adverse effect risk; and determining an antibiotic dose and an antibiotic treatment schedule, each adapted so that, when the antibiotic is administered to the patient at the antibiotic dosage amount according to the antibiotic treatment schedule, a circulating level of the antibiotic is predicted to be achieved in the patient that is safe and therapeutically effective to treat the infection in the patient and administering

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the antibiotic to the patient at the antibiotic dosage amount according to the antibiotic treatment schedule while concomitantly administering colchicine to the patient at a polytherapy colchicine dosage amount that is a fraction less than or equal to  $\frac{1}{2}$  of the monotherapy colchicine dosage amount to the patient according to the colchicine treatment schedule.

According to this embodiment, upon the administering of the antibiotic to the patient at the antibiotic dosage amount according to the antibiotic treatment schedule while concomitantly administering colchicine to the patient at the polytherapy colchicine dose according to the colchicine treatment schedule, the therapeutic circulating level of colchicine is achieved in the patient. Preferably, the fraction is selected from  $\frac{1}{12}$ ,  $\frac{1}{6}$ ,  $\frac{1}{4}$ ,  $\frac{1}{3}$ ,  $\frac{5}{12}$ , and  $\frac{1}{2}$ , more preferably, the fraction is  $\frac{1}{3}$  or  $\frac{1}{2}$ . Preferably the antibiotic is selected from clarithromycin, dirithromycin, erythromycin and roxithromycin. Exemplary conditions are selected from gout, FMF, thrombocytopenic purpura, and Behçet's disease. In a preferred embodiment, the gout is an acute gout flare and the colchicine treatment schedule is an acute treatment schedule adapted for treatment of acute gout flares, or the gout is chronic gout, and the colchicine treatment schedule is a chronic treatment schedule adapted for prophylaxis of flares. In another embodiment, the fraction is  $\frac{1}{3}$  or  $\frac{1}{2}$  and treatment with colchicine is initiated subsequent to initiation of treatment with clarithromycin.

In one embodiment, each of the monotherapy colchicine doses and the colchicine treatment schedule are each adapted so that, when colchicine is administered to the patient at the monotherapy colchicine dose according to the colchicine treatment schedule in the absence of concomitant administration of the antibiotic, a therapeutic circulating level of colchicine is predicted to be achieved in the patient that is predicted to be safe and effective to treat the condition in the patient while posing an acceptable adverse effect risk.

Alternately, the antibiotic dose and the antibiotic treatment schedule are each adapted so that, when the antibiotic is administered to the patient at the antibiotic dose according to the antibiotic treatment schedule a circulating level of the antibiotic is predicted to be achieved in the patient that is therapeutically effective to treat the infection in the patient.

In one embodiment, upon the administration of the antibiotic to the patient at the antibiotic dose according to the antibiotic treatment schedule while concomitantly administering colchicine to the patient according to the colchicine treatment schedule at the polytherapy colchicine dose, a therapeutic circulating level of colchicine is predicted to be achieved in the patient that is predicted to be safe and effective to treat the condition in the patient while posing an acceptable adverse effect risk. In one embodiment, each subsequent colchicine dose is the same as the second colchicine dose. In another embodiment, each of the second and subsequent colchicine doses are the same as the first colchicine dosage amounts. In another, the fraction is selected from about  $\frac{1}{12}$ , about  $\frac{1}{6}$ , about  $\frac{1}{4}$ , about  $\frac{1}{3}$ , about  $\frac{5}{12}$ , about  $\frac{1}{2}$ , and about  $\frac{7}{12}$ , e.g., about  $\frac{1}{2}$  or about  $\frac{2}{3}$ . In certain embodiments, the colchicine treatment schedule is once-a-day, twice-a-day, three-times-a-day or four-times-a-day.

#### 60 Acute Gout

Acute gout, or gout flares, can be treated according to the following treatment schedule. This table indicates the original, or intended, dosage amount, i.e., the dosage amount of colchicine recommended absent concomitant administration of the drugs listed below. This table also presents the dosage amount adjustment, or the recommended colchicine dosage amount to be administered when strong and moderate

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CYP3A4 and P-gp inhibitors are administered concomitantly with colchicine when the patient is being treated for a gout flare.

Colchicine Dose Recommendation		
Drug	Original Intended Dose (Total Dose)	Dose Adjustment
Regimen Reduced by Two Thirds		
Strong CYP3A4 Inhibitors		
Clarithromycin	1.2 mg (2 tablets) at the first sign of the flare followed by 0.6 mg (1 tablet) one hour later.	0.6 mg (1 tablet) × 1 dose. Dose to be repeated no earlier than 3 days.
Erythromycin	Dose to be repeated no earlier than 3 days.	

#### Chronic Gout

For chronic gout (prophylaxis of gout flares), an original intended daily dosage amount is 1.2 mg or 6 mg. Alternatively, an intended daily dosage amount of chronic gout can be as much as 2.4 mg per day. The daily dosage amount for chronic gout can be administered at one time or dosed at intervals throughout the day, e.g. twice daily, three times daily, or four times daily.

Chronic gout, with and without a concomitant dose of another drug, can be treated according to the following treatment schedule:

#### Colchicine Dose Adjustment for Co-administration with Interacting Drugs if No Alternative Available

Colchicine Dose Recommendation		
Drug	Original Intended Dose	Dose Adjustment
Clarithromycin	0.6 mg twice daily	0.3 mg once daily
	0.6 mg once daily	0.3 mg once every other day
Erythromycin	0.6 mg twice daily	0.3 mg once daily
	0.6 mg once daily	0.3 mg once every other day

The dosage amount of 0.3 mg once every other day is administered either as 0.3 mg once every other day or 0.15 mg once a day.

#### Familial Mediterranean Fever

Familial Mediterranean Fever (FMF) can be treated according to the following intended daily dosing schedule:

Daily dosage amount		
Age	Usual	Maximum
Adults and children >12 years	1.2 mg	2.4 mg
Children >6 to 12 years	0.9 mg	1.8 mg
Children 4 to 6 years	0.3 mg	1.8 mg

When colchicine is given to patients with FMF concomitantly with other drugs, the adjusted (reduced) dosage amount of colchicine, according to this embodiment, is provided in the table below:

Concomitant Drug Class or Food	Noted or Anticipated Outcome	Clinical Comment
Strong CYP3A4 Inhibitors:	Significant increase in colchicine plasma	Use colchicine with caution at reduced

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-continued

Concomitant Drug Class or Food	Noted or Anticipated Outcome	Clinical Comment
5 clarithromycin	levels <sup>1</sup> ; fatal colchicine toxicity has been reported with clarithromycin, a strong CYP3A4 inhibitor. Similarly, significant increase in colchicine plasma levels is anticipated with other strong CYP3A4 inhibitors.	maximum dose of 0.3 mg twice daily with increased monitoring for adverse effects. In patients with renal or hepatic impairment, use of colchicine in conjunction with these drugs is contraindicated.
10 Moderate CYP3A4 inhibitors:	Significant increase in colchicine plasma concentration is anticipated.	Use colchicine with caution at reduced maximum dose of 0.6 mg twice daily with increased monitoring for adverse effects. In patients with renal or hepatic impairment, use a maximum dose of 0.3 mg twice daily.
15 erythromycin	Neuromuscular toxicity has been reported with diltiazem and verapamil interactions.	
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Colchicine is one of the most widely used drugs for treating familial Mediterranean fever (FMF). It has been reported that 5-10% of FMF patients do not show a beneficial response to colchicine administration. A polymorphism in the ABCB1 gene, the "ABCB1 3435 C to T polymorphism" has been reported to correlate with this lack of response to colchicine treatment, with patients with the homozygous TT genotype exhibiting the most pronounced "non-responder" phenotypes.

Accordingly, in another aspect, provided herein is a method for treating a patient suffering from FMF, which patient is a colchicine non-responder. In one embodiment, the patient is homozygous for the TT genotype of the ABCB1 3435 C to T polymorphism. The method entails the concomitant administration of a Pgp inhibitor and colchicine to the patient. A preferred Pgp inhibitor for use in this method is verapamil or cyclosporine-A, more preferably a macrolide antibiotic, preferably dirithromycin, erythromycin or roxithromycin, or, more preferably clarithromycin. Dosage amounts of the Pgp inhibitor for this purpose correspond to those called for in the prescribing information for the drug in question. For clarithromycin, the dosage amounts are 500 to 1000 mg per day and duration of clarithromycin dosing is preferably one, two, or three days, repeated weekly or bi-weekly. Preferred colchicine dosing regimens for this purpose are the same as used for treatment of FMF in responders, though the doses of colchicine administered may be increased as tolerated, e.g., up to two to three times the typical doses.

These and other embodiments, advantages and features of the present invention are further elaborated herein below.

#### DETAILED DESCRIPTION

Following multiple oral doses (0.6 mg twice daily), the mean elimination half-life of colchicine in young healthy volunteers (mean age 25 to 28 years of age) is 26.6 to 31.2 hours.

Pharmacy management systems are computer-based systems that are widely used by commercial pharmacies to manage prescriptions and to provide pharmacy and medical personnel with warnings and guidance regarding drugs being administered to patients. Such systems typically provide alerts warning either or both of health care providers and patients when a drug that may be harmful to the particular

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patient is prescribed. For example, such systems can provide alerts warning that a patient has an allergy to a prescribed drug, or is receiving concomitant administration of a drug that can have a dangerous interaction with a prescribed drug. U.S. Pat. Nos. 5,758,095, 5,833,599, 5,845,255, 6,014,631, 6,067, 524, 6,112,182, 6,317,719, 6,356,873, and 7,072,840, each of which is incorporated herein by reference, disclose various pharmacy management systems and aspects thereof. Many pharmacy management systems are now commercially available, e.g., CENTRICITY Pharmacy from BDM Information Systems Ltd., General Electric Healthcare, Waukesha, Wis., Rx30 Pharmacy Systems from Transaction Data Systems, Inc., Ocoee, Fla., SPEED SCRIPT from Digital Simplicities, Inc., Lenexa, Kans., and various pharmacy management systems from OPUS-ISM, Hauppauge, N.Y.

In the specification and claims that follow, references will be made to a number of terms which shall be defined to have the following meaning.

The terms “a” and “an” do not denote a limitation of quantity, but rather denote the presence of at least one of the referenced item. The term “or” means “and/or”. The terms “comprising”, “having”, “including”, and “containing” are to be construed as open-ended terms (i.e., meaning “including, but not limited to”).

“Concomitant” and “concomitantly” as used herein refer to the administration of at least two drugs to a patient either simultaneously or within a time period during which the effects of the first administered drug are still operative in the patient. Thus, if the first drug is, e.g., clarithromycin and the second drug is colchicine, the concomitant administration of the second drug can occur as much as one to two weeks, preferably within one to seven days, after the administration of the first drug. This is because clarithromycin can exert a long-lasting inhibition of CYP3A isozymes so that CYP3A activity in the patient may not return to pre-clarithromycin-administration levels for as much as two weeks after the cessation of clarithromycin administration. If colchicine is the first drug, administration of a second drug would be concomitant if done within 1 to 2 days, preferably 12 to 24 hours.

“Dosage amount” means an amount of a drug suitable to be taken during a fixed period, usually during one day (i.e., daily).

“Dosage amount adapted for oral administration” means a dosage amount that is of an amount deemed safe and effective for the particular patient under the conditions specified. As used herein and in the claims, this dosage amount is determined by following the recommendations of the drug manufacturer’s Prescribing Information as approved by the US Food and Drug Administration.

“Dosing regimen” means the dose of a drug taken at a first time by a patient and the interval (time or symptomatic) and dosage amounts at which any subsequent doses of the drug are taken by the patient. Each dose may be of the same or a different dosage amount.

A “dose” means the measured quantity of a drug to be taken at one time by a patient.

A “patient” means a human or non-human animal in need of medical treatment. Medical treatment can include treatment of an existing condition, such as a disease or disorder, prophylactic or preventative treatment, or diagnostic treatment. In preferred embodiments the patient is human.

“Providing” means giving, administering, selling, distributing, transferring (for profit or not), manufacturing, compounding, or dispensing.

“Risk” means the probability or chance of adverse reaction, injury, or other undesirable outcome arising from a

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medical treatment. An “acceptable risk” means a measure of the risk of harm, injury, or disease arising from a medical treatment that will be tolerated by an individual or group. Whether a risk is “acceptable” will depend upon the advantages that the individual or group perceives to be obtainable in return for taking the risk, whether they accept whatever scientific and other advice is offered about the magnitude of the risk, and numerous other factors, both political and social. An “acceptable risk” of an adverse reaction means that an individual or a group in society is willing to take or be subjected to the risk that the adverse reaction might occur since the adverse reaction is one whose probability of occurrence is small, or whose consequences are so slight, or the benefits (perceived or real) of the active agent are so great. An “unacceptable risk” of an adverse reaction means that an individual or a group in society is unwilling to take or be subjected to the risk that the adverse reaction might occur upon weighing the probability of occurrence of the adverse reaction, the consequences of the adverse reaction, and the benefits (perceived or real) of the active agent. “At risk” means in a state or condition marked by a high level of risk or susceptibility.

Pharmacokinetic parameters referred to herein describe the in vivo characteristics of drug (or a metabolite or a surrogate marker for the drug) over time. These include plasma concentration (C), as well as  $C_{max}$ ,  $C_n$ ,  $C_{24}$ ,  $T_{max}$ , and AUC. “ $C_{max}$ ” is the measured plasma concentration of the active agent at the point of maximum, or peak, concentration. “ $C_{min}$ ” is the measured plasma concentration of the active agent at the point of minimum concentration. “ $C_n$ ” is the measured plasma concentration of the active agent at about n hours after administration. “ $C_{24}$ ” is the measured plasma concentration of the active agent at about 24 hours after administration. The term “ $T_{max}$ ” refers to the time from drug administration until  $C_{max}$  is reached. “AUC” is the area under the curve of a graph of the measured plasma concentration of an active agent vs. time, measured from one time point to another time point. For example  $AUC_{0-t}$  is the area under the curve of plasma concentration versus time from time 0 to time t, where time 0 is the time of initial administration of the drug. Time t can be the last time point with measurable plasma concentration for an individual formulation. The  $AUC_{0-\infty}$  or  $AUC_{0-INF}$  is the calculated area under the curve of plasma concentration versus time from time 0 to time infinity. In steady-state studies,  $AUC_{0-\tau}$  is the area under the curve of plasma concentration over the dosing interval (i.e., from time 0 to time  $\tau$  (tau), where tau is the length of the dosing interval. Other pharmacokinetic parameters are the parameter  $K_e$  or  $K_{el}$ , the terminal elimination rate constant calculated from a semi-log plot of the plasma concentration versus time curve;  $t_{1/2}$  the terminal elimination half-life, calculated as  $0.693/K_{el}$ .  $CL/F$  denotes the apparent total body clearance after administration, calculated as Total Dose/Total  $AUC_{\infty}$ ; and  $V_{area}/F$  denotes the apparent total volume of distribution after administration, calculated as Total Dose/(Total  $AUC_{\infty} \times K_{el}$ ).

“Side effect” means a secondary effect resulting from taking a drug. The secondary effect can be a negative (unfavorable) effect (i.e., an adverse side effect) or a positive (favorable) effect.

The most frequently reported adverse side effects to colchicine therapy are gastrointestinal, specifically abdominal pain with cramps, diarrhea, nausea, and vomiting. Less frequently or rarely reported adverse side effects associated with colchicine therapy include anorexia, agranulocytosis, allergic dermatitis, allergic reactions, alopecia, angioedema, aplastic anemia, bone marrow depression, myopathy, neuropathy, skin rash, thrombocytopenic disorder, and urticaria.

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Whether a patient experiences an adverse side effect can be determined by obtaining information from the patient regarding onset of certain symptoms which may be indicative of the adverse side effect, results of diagnostic tests indicative of the adverse side effect, and the like.

The following examples further illustrate aspects of this disclosure but should not be construed as in any way limiting its scope. In particular, the conditions are merely exemplary and can be readily varied by one of ordinary skill in the art.

## EXAMPLES

## Example 1

## Pharmacokinetic Study in Healthy Adults of Single Vs. Multiple Oral Doses of Colchicine Tablets

This study was a single-center, open-label, single-sequence, two-period study to evaluate the pharmacokinetic profile of colchicine following single and multiple oral doses of colchicine tablets, 0.6 mg, in healthy volunteers.

In Period 1, study subjects received a 0.6-mg dose of colchicine after an overnight fast of at least 10 hours. In Period 2, subjects received a 0.6-mg dose of colchicine in the morning and the evening (approximately 12 hours later) for 10 days (steady state regimen). Subjects received a light breakfast served 60 minutes following dose administration in the morning and the evening dose was administered 90 minutes after an evening meal on Days 15 through 24 only. On Day 25, the colchicine dose was administered after an overnight fast of at least 10 hours and lunch was served 4 hours post-dose. Study periods were separated by a 14-day wash-out. Following the single dose and the last dose of the multiple dose regimen (beginning on the mornings of Day 1 and Day 25, respectively), blood samples were collected (6 mL each) from each subject within 1 hour prior to dosing and after dose administration at study hours 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 (while confined) and 36, 48, 72, and 96 (on an outpatient basis). Plasma concentrations of colchicine and its metabolites were determined using validated LC/MS-MS methods.

Thirteen healthy, non-smoking subjects with a mean age of 25.5 years (range 19 to 38 years) and within 15% of ideal body weight were enrolled in this study. All subjects completed both dosing periods according to protocol.

After a single dose, plasma concentrations are no longer quantifiable 24 hours post-dose in all but 1 subject. After the last dose of the steady state regimen, concentrations remained quantifiable for 48 to 72 hours. Review of individual subject data shows that no subject experienced a secondary colchicine peak, either following a single dose or upon multiple dosing.

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All 2-O-demethylcolchicine (2-DMC) concentrations were below the level of quantitation (LOQ, 0.2 ng/mL) and only one sample from 1 subject (of 13 subjects) had a detectable 3-O-demethylcolchicine (3-DMC) concentration, which was near the level of quantitation. Therefore, metabolites are not discussed further.

In healthy adults, colchicine appears to be readily absorbed when given orally, reaching a mean maximum plasma concentration of 2.5 ng/mL in 1.5 hours after a single dose. The drug is distributed widely, with an apparent volume of distribution of 540 L, greatly exceeding total body water. The elimination half-life as calculated following a single oral dose is approximately 5 hours. Levels were not detectable by 24 hours post-dose and this is therefore not an accurate estimate. Pharmacokinetic parameter values are summarized in the table below.

Review of trough plasma concentrations indicates that steady state was attained by approximately the eighth day of dosing for most subjects. Colchicine may have a diurnal variation reflected in the observed C<sub>min</sub> concentrations at steady state. C<sub>min</sub> concentrations prior to the morning dose are approximately 12% higher than the C<sub>min</sub> concentrations prior to the evening dose (Day 23 and Day 24). The mean C<sub>min</sub> concentration observed on Day 25 was 0.907 ng/mL.

Colchicine accumulated following administration of multiple doses to an extent greater than expected. Exposure was nearly two-fold higher (approximately 1.7 based on AUC [Day 25 AUC<sub>0-∞</sub>/Day 1 AUC<sub>0-∞</sub>]) and approximately 1.5 based on C<sub>max</sub> [Day 25 C<sub>max</sub>/Day 1 C<sub>max</sub>]). This observation could be attributable to an underestimation of AUC<sub>∞</sub> following a single dose. With the higher plasma levels that occur with repeated dosing, a longer terminal elimination half life is apparent, 26.6 hours. Pharmacokinetic parameter values are summarized in the tables below.

TABLE 1

Colchicine Pharmacokinetic Parameter Values Following Administration of A Single Oral Dose of Colchicine 0.6 mg in Healthy Adults (N = 13)

	AUC <sub>0-t</sub> (pg-hr/mL)	AUC <sub>0-∞</sub> (pg-hr/mL)	C <sub>max</sub> (pg/mL)	T <sub>max</sub> (hr)	K <sub>el</sub> (1/hr)	T <sub>1/2</sub> (hr)
MEAN	10508.54	12281.90	2470.77	1.50	0.1829	4.95
STDEV	3544.82	4423.34	706.98	0.54	0.0592	4.43
% CV	33.73	36.02	28.61	36.00	32.39	89.54
MEDIAN	10560.90	11451.45	2714.00	1.50	0.1992	3.48
MIN	4812.88	7252.66	1584.00	1.00	0.0359	2.84
MAX	18128.65	23838.48	3977.00	3.00	0.2443	19.29

TABLE 2

Colchicine Pharmacokinetic Parameter Values Following Administration of Multiple (b.i.d.) Oral Doses of Colchicine 0.6 mg in Healthy Adults (N = 13)

	AUC <sub>0-t</sub> (pg-hr/mL)	AUC <sub>0-∞</sub> (pg-hr/mL)	AUC <sub>0-∞</sub> (pg-hr/mL)	C <sub>max</sub> (pg/mL)	C <sub>min</sub> (pg/mL)	C <sub>ave</sub> (pg/mL)	T <sub>max</sub> (hr)	K <sub>el</sub> (1/hr)	T <sub>1/2</sub> (hr)
MEAN	43576.96	29056.23	54198.77	3553.15	906.51	1210.68	1.31	0.03	26.60
STDEV	9333.26	4531.30	9214.54	843.45	152.19	188.80	0.60	0.00	4.33
% CV	21.42	15.59	17.00	23.74	16.79	15.59	45.61	16.34	16.26
MEDIAN	41925.10	28452.15	54113.43	3734.00	903.50	1185.51	1.00	0.03	26.51
MIN	29328.78	20791.98	37599.76	1977.00	636.23	866.33	0.50	0.02	20.82
MAX	58265.35	36083.95	67944.65	4957.00	1149.67	1503.50	3.00	0.03	33.65

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TABLE 3

Mean (% CV) Colchicine Pharmacokinetic Parameter Values Following Administration of Single and Multiple (b.i.d.) Oral Doses of Colchicine 0.6 mg in Healthy Adults		
	Vd/F (L)	CL/F (L/hr)
Colchicine 0.6 mg Single Dose (N = 13)		
Day 1	540.5 (31.0)	341.5 (54.4)
Colchicine 0.6 mg b.i.d. × 10 days		
Day 25	1150 (18.73)	30.3 (19.0)

CL = Dose/AUC<sub>0-τ</sub> (Calculated from mean values)

Vd = CL/Ke (Calculated from mean values)

In the above table, the parameter CL/F denotes the apparent total body clearance after administration, calculated as Total Dose/Total AUC<sub>0-τ</sub>; and V<sub>d</sub>/F denotes the apparent total volume of distribution after administration, calculated as Total Dose/(Total AUC<sub>∞</sub> × K<sub>el</sub>).

## Example 2

## Clinical Drug-Drug Interaction Study of Colchicine and Clarithromycin

A single-center, open-label, one sequence, two-period study was carried out in 23 healthy subjects. On Day 1, a single 0.6-mg dose of colchicine was administered. After completing a 21-day washout period, all subjects received 250 mg of clarithromycin administered twice daily for 7 days (Days 22 through 29), a sufficient dose and duration to inhibit CYP3A4 and Pgp. On the final day (Day 29), a single dose of colchicine was co-administered with the clarithromycin dose.

When combined with steady-state clarithromycin, there is a significant increase in exposure to colchicine as compared to when colchicine is given alone: the mean C<sub>max</sub> and AUC<sub>0-τ</sub> concentrations increased 167% and 250%, respectively. In addition, co-administration of clarithromycin and colchicine resulted in an increase of 233% in the plasma elimination half-life (t<sub>1/2</sub>) of colchicine and a 75% decrease in apparent clearance (CL/F). A summary of the mean (% CV) colchicine pharmacokinetic parameters for Day 1 (colchicine administered alone) and Day 29 (colchicine co-administered with steady-state clarithromycin) are given in the table below and illustrated in the table that follows.

TABLE 4

Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Clarithromycin in Healthy Adults								
DAY	C <sub>max</sub> (ng/mL)	T <sub>max</sub> <sup>1</sup> (h)	AUC <sub>0-τ</sub> (ng · h/mL)	AUC <sub>∞</sub> (ng · h/mL)	Ke (h <sup>-1</sup> )	Vd/F (L)	CL/F (L/hr)	t <sub>1/2</sub> (h)
Colchicine Alone (n = 23)								
1	3 (30.97)	1.00 (0.5-2.0)	12 (37.6)	16 (49.6)	0.132 (46.87)	432 (56.1)	46.8 (43.7)	9 (126.4)
Colchicine + Clarithromycin (n = 23)								
29	8 (23.74)	1.0 (1.0-5.0)	42 (23.3)	53 (22.8)	0.0298 (90.82)	493 (33.69)	12 (23.8)	30 (41.37)
p value								
	<0.0001	0.05061	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.0001

<sup>1</sup>T<sub>max</sub> mean (range)

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Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. The endpoints of all ranges directed to the same component or property are inclusive and independently combinable.

All methods described herein can be performed in a suitable order unless otherwise indicated or clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") herein is intended to better illuminate the disclosure and is non-limiting unless otherwise specified. No language in the specification should be construed as indicating that any non-claimed element as essential to the practice of the claimed embodiments. Unless defined otherwise, technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this disclosure belongs. The terms wt %, weight percent, percent by weight, etc. are equivalent and interchangeable.

Embodiments are described herein, including the best modes known to the inventors. Variations of such embodiments will become apparent to those of ordinary skill in the art upon reading the foregoing description. The skilled artisan is expected to employ such variations as appropriate, and the disclosed methods are expected to be practiced otherwise than as specifically described herein. Accordingly, all modifications and equivalents of the subject matter recited in the claims appended hereto are included to the extent permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed unless otherwise indicated herein or otherwise clearly contradicted by context.

What is claimed is:

1. A method of using colchicine for prophylactic treatment of gout flares in an adult human gout patient so as to reduce the occurrence of colchicine toxicity when said patient is receiving concomitant administration of clarithromycin, said method comprising:

orally administering a reduced colchicine daily dosage amount to the patient for prophylactic treatment of gout flares, wherein the reduced colchicine daily dosage amount is a 75% reduction of a colchicine dosage amount adapted for oral administration to the gout patient for the prophylaxis of gout flares in the absence of concomitant administration of clarithromycin,

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wherein concomitant administration of clarithromycin is administration within 1 to 2 days of orally administering the second colchicine dosage amount.

2. The method of claim 1, wherein the colchicine dosage amount adapted for oral administration to the gout patient for the prophylaxis of gout flares in the absence of concomitant administration of clarithromycin is 0.6 mg twice per day.

3. The method of claim 2, wherein the reduced colchicine dosage amount is 0.3 mg once per day.

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4. The method of claim 1, wherein the colchicine dosage amount adapted for oral administration to the gout patient for the prophylaxis of gout flares in the absence of concomitant administration of clarithromycin is 0.6 mg once per day.

5. The method of claim 4, wherein the reduced colchicine dosage amount is 0.3 mg once every other day.

\* \* \* \* \*

UNITED STATES PATENT AND TRADEMARK OFFICE  
**CERTIFICATE OF CORRECTION**

PATENT NO. : 8,097,655 B2  
APPLICATION NO. : 13/109034  
DATED : January 17, 2012  
INVENTOR(S) : Matthew W. Davis

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It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On Title page 2, Item (56), under "OTHER PUBLICATIONS", line 3, delete "Wikidpedia" and insert -- Wikipedia --, therefor.

On Title page 2, Item (56), under "OTHER PUBLICATIONS", line 4, delete "Achert;" and insert -- Achtert; --, therefor.

In column 1, line 12, delete "continuation of part" and insert -- continuation-in-part --, therefor.

In column 3, line 27, delete "*phila.*" and insert -- *phila*, --, therefor.

In column 3, line 32, delete "100" and insert -- 1000 --, therefor.

In column 4, line 14, delete "3-demethylchochicine" and insert -- 3-demethylcolchicine --, therefor.

In column 4, lines 31-32, delete "3-demethylchochicine" and insert -- 3-demethylcolchicine --, therefor.

In column 6, line 22, delete "□" and insert -- ■ --, therefor.

In column 6, line 50, delete "in suffering" and insert -- suffering --, therefor.

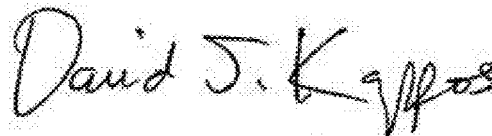
In column 7, line 21, delete "6" and insert -- 5 --, therefor.

In column 7, line 23, delete "7" and insert -- 6 --, therefor.

In column 7, line 24, delete "8" and insert -- 7 --, therefor.

In column 7, line 26, delete "9" and insert -- 8 --, therefor.

Signed and Sealed this  
Twenty-third Day of October, 2012

A handwritten signature in black ink, reading "David J. Kappos". The signature is written in a cursive, flowing style with a large initial 'D' and 'K'.

David J. Kappos  
Director of the United States Patent and Trademark Office

**CERTIFICATE OF CORRECTION (continued)**

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In column 7, line 28, delete “10” and insert -- 9 --, therefor.

In column 10, line 44, delete “a one” and insert -- one --, therefor.

In column 12, line 4, delete “a one” and insert -- one --, therefor.

In column 13, line 3, after “clarithromycin” insert -- and --.

In column 15, line 21, delete “6” and insert -- 0.6 --, therefor.

In column 15, line 22, delete “of” and insert -- for --, therefor.

In column 16, line 5, delete “levels<sup>1</sup>” and insert -- levels --, therefor.

In column 20, line 4, delete “3-O-demethylcolchicine” and insert -- 3-O-demethylcolchicine --, therefor.

In column 21, line 6, delete “V<sub>d</sub>/F” and insert -- V<sub>d</sub>/F --, therefor.

In column 21, line 9, delete “540.5 (31.0)” and insert -- 341 (54.4) --, therefor.

In column 21, line 9, delete “341.5 (54.4)” and insert -- 54.1 (31.0) --, therefor.

In column 21, line 14, delete “V<sub>d</sub>=CL/K<sub>e</sub>” and insert -- V<sub>d</sub>=CL/K<sub>e</sub> --, therefor.

In column 21, line 18, delete “AUC<sub>0- $\tau$ ” and insert -- AUC<sub>0- $\tau$  --, therefor.</sub></sub>

In column 21, line 43, delete “t<sub>1/2</sub>” and insert -- t<sub>1/2</sub> --, therefor.

In column 21, lines 47-48, delete “table below and illustrated in the table that follows.” and insert -- table below. --, therefor.

In column 21, line 54, delete “K<sub>e</sub>” and insert -- K<sub>e</sub> --, therefor.

In column 21, line 54, delete “V<sub>d</sub>/F” and insert -- V<sub>d</sub>/F --, therefor.

In column 22, line 21, after “interchangeable” insert -- . --.